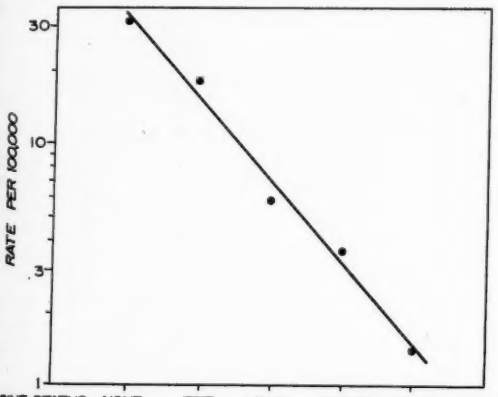
PERSISTENCE OF IMMUNITY AFTER ADMINISTRATION OF FORMALIN-TREATED POLIOVIRUS VACCINE *

JONAS E. SALK
M.D. New York Univ.
DIRECTOR OF VIRUS RESEARCH LABORATORY AND COMMONWEALTH PROFESSOR OF EXPERIMENTAL MEDICINE AT THE UNIVERSITY OF PITTSBURGH
From the School of Medicine, Pittsburgh, Pennsylvania

A PROPER appreciation of the question of persistence of immunity following administration of a formalin-treated poliovirus vaccine requires an understanding of the factors that influence the initiation of immunity.

Initiation of Immunity

An interesting approach is afforded by experience in the United States in 1959, when cases of paralytic poliomyelitis were sufficiently widespread and numerous to permit comparison of the relative efficacy of different numbers of doses.



VACCINE STATUS	NONE	ONE	TWO	THREE	FOUR	Doses
Estim. Population (millions)	4.7	1.3	3.6	7.4	3.6	
Number of Cases	1508	234	209	267	51	
Rate/100,000	32.1	18.0	5.8	3.6	1.4	

Fig. 1—1959 paralysis-rate in age-group 0–4 years.

NUMBER OF INJECTIONS

During the year, 5267 cases of poliomyelitis with residual paralysis were recorded (Langmuir 1960). Of these, 2269 were in the age-group 0–4 years, and their vaccination status was as shown in fig. 1. This reveals an inverse linear relationship between the paralysis-rate (plotted on a logarithmic scale) and the number of doses administered at unspecified times.

Fig. 2, containing similar data for the age-groups 5–19 and 20–39, shows a reasonably good alignment of points for those receiving one or more doses of vaccine. For the unvaccinated in these age-groups, however, the non-alignment of the points suggests the possible operation of the factors revealed by Francis in the 1954 field trial, in which the incidence of poliomyelitis was lower in the observed-controls than in the placebo-controls (Francis et al. 1957). As in that trial, a lower socioeconomic status might account for a lower-than-expected relative incidence of paralytic poliomyelitis in the unvaccinated. In the 0–4 age-group (fig. 2) the approximation of all of the observed points to a straight line suggests that, in the early years of life in the United States, susceptibility is more uniform, and less affected by status. The data from which figs. 1 and 2 were constructed are given in the table. Reasons for non-alignment of the lowest point for the 20–39 age-group come to mind, but the number of cases is too small for useful comment.

Type-1 virus was identified in 89·5% of the 3910 cases in which poliovirus was isolated (Langmuir 1960). Type-3 virus was found in 10·1% and type-2 virus in 0·4%. In view of this preponderance of type-1 virus, the overall effect of vaccination revealed in figs. 1 and 2 may be considered to reflect principally the efficacy of the type-1 component of vaccine used during the period in question.

It is clear from fig. 1 that in part of the vaccinated population even a single dose of vaccine conferred immunity. The linear relationship indicates that each successive dose reduced the remainder of the susceptibles by the same proportion as did the first dose. If this example represents a general rule for vaccines that induce immune conversion in only a proportion of those vaccinated, its significance can be further appreciated by examining a series of hypothetical curves describing the cumulative percent conversions assumed to take place after successive doses of vaccines of different one-dose conversion efficiencies. This is illustrated in fig. 3, where the cumulative percent conversion is plotted in relation to number of doses. The 1959 paralysis-rate data from fig. 1, converted to percent effectiveness, are also plotted in fig. 3. Their relation to the hypothetical curves indicates

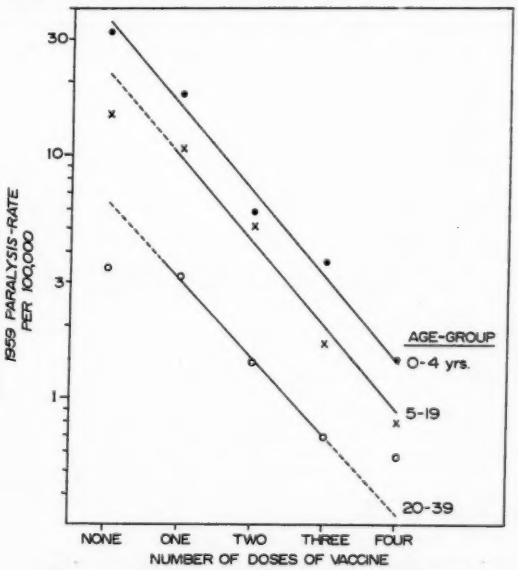


Fig. 2—Paralysis-rate according to vaccination status.

* Presented in part at the Fifth International Poliomyelitis Conference, Copenhagen, on July 27, 1960.

NUMBER OF CASES AND PARALYSIS-RATE ACCORDING TO VACCINATION STATUS IN UNITED STATES IN 1959

Age-group and vaccination status	Estimated * population September, 1959 (thousands)	Paralytic poliomyelitis †	
		Number of cases	Rate per 100,000
0–4			
0	4700	1508	32·09
1	1300	234	18·00
2	3600	209	5·81
3	7400	267	3·61
4+	3600	51	1·42
Total	20,600	2269	11·01
5–19			
0	6800	997	14·66
1	1500	159	10·60
2	3900	198	5·08
3	23,300	390	1·67
4+	12,600	99	0·79
Total	48,100	1843	3·83
20–39			
0	22,800	787	3·45
1	2000	64	3·20
2	4800	67	1·40
3	12,400	86	0·69
4+	4600	26	0·57
Total	46,600	1030	2·21

* Based on random survey of 17,500 families, Census Bureau, September 1959.
† Final report corrected for 60-day follow-up.
Source: U.S. Public Health Service, poliomyelitis surveillance report no. 197, May 16, 1960.

that, in 1959, the average effect for a single dose was more than 50%. The curves for vaccines of low potency suggest that, with progressive decline in one-dose effect, multiple doses of weak vaccine become less and less efficient for immunisation. Conversely, the greatest efficiency is associated with vaccines that approximate a full effect after one dose.

Fig. 4 shows the data for 1959, plotted logarithmically, along with illustrations of hypothetical cumulative immune-conversions assumed for vaccines that induce 60, 75, or 90% conversion after a single dose. It illustrates somewhat more pointedly than fig. 3 the diminishing returns of successive doses of relatively weak vaccine, and the greater efficiency of more potent vaccine. Like fig. 1, it also shows that the cumulative increase in immunes is augmented after each dose as though those who did not respond initially do respond to later doses—with the same probability of conversion as if they were being treated for the first time with vaccine of that potency. These relationships suggest that immunity results from the first effective antigenic stimulus; and that, if the first dose does not induce immunity, a critical level may be reached after subsequent doses. They also suggest that, if a critical level of response can be achieved after one injection, then uniform immunisation by one dose of a killed-virus vaccine is theoretically possible.

In considering how far paralytic poliomyelitis occurring in triply vaccinated people is due to failure to induce an immune response initially, and how far it is due to waning immunity, it is helpful to examine more closely the relationships illustrated in fig. 4. Clearly, with each additional dose a greater proportion of the vaccinated population was protected, protection reaching about 92% after three doses and about 96% after four. If the dosage-response line, as drawn in fig. 4, is projected, a fifth dose should increase the proportion of immunes by approximately 2%, and a sixth would add a further 1%, still leaving about 1% unprotected. The use, for any dose, of vaccines of 75% or 90% conversion-efficiency in one dose would cause more vertical deflections as shown by the hypothetical projections after the fourth dose. The diminishing return of successive doses emphasises the desirability of achieving the highest level of immunisation with the fewest injections.

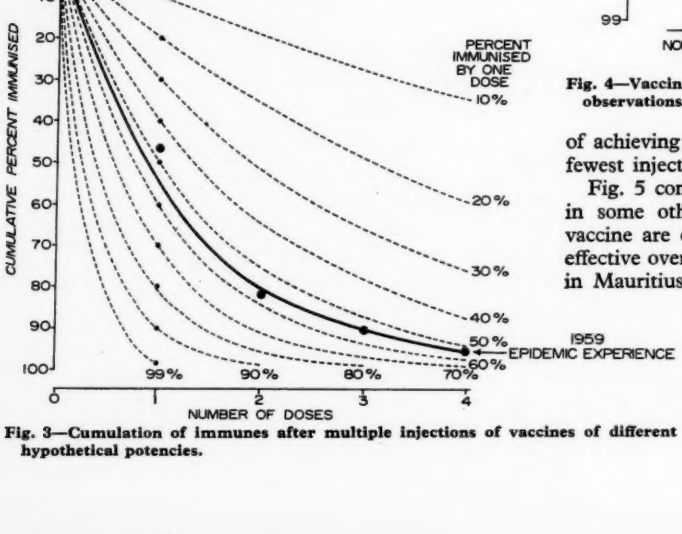


Fig. 3—Cumulation of immunes after multiple injections of vaccines of different hypothetical potencies.

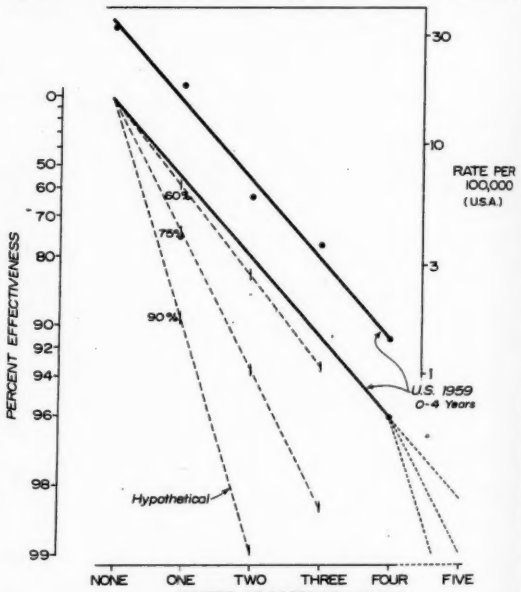


Fig. 4—Vaccines of different hypothetical potencies compared with observations in 0–4 age-groups.

Fig. 5 compares experience in the United States and in some other countries. In Belgium three doses of vaccine are estimated to have been approximately 95% effective over a two-year period (Prinzie et al. 1960), and in Mauritius a single severe outbreak revealed approximately 99% protection by three doses (Poliomyelitis Surveillance Unit 1960). The probable one-dose effects of the average of the vaccine used in these areas may be deduced from this graph. In Sweden, Olin (1960) has reported 97% effectiveness for three doses—the first two largely

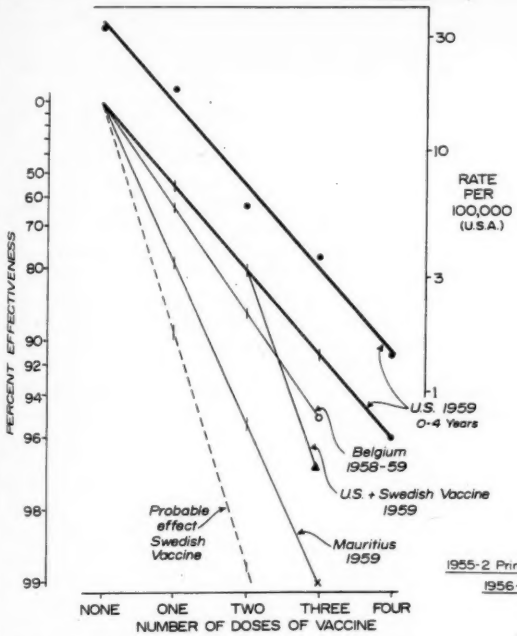


Fig. 5—Comparison of effectiveness in selected instances.

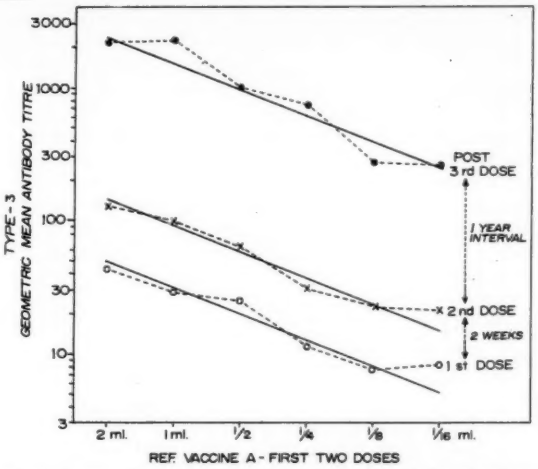


Fig. 6—Dosage response effect. Type-3 antibody levels 2 weeks after each dose.

from United States sources and the third made in Sweden. If the effect of the first two doses of vaccine used in Sweden was the same as the average effect of vaccine used in the United States, Swedish vaccine used for the third dose can be interpreted as having been approximately 85–90% effective in a single dose (as suggested by a line from the 0-point and parallel to the line drawn between the second-dose and the third-dose points). If the average potency of American vaccine used in Sweden was greater than the overall United States average, then 97% protection could have followed the third dose even if the Swedish vaccine had been of somewhat lesser potency. These examples indicate the possible usefulness of this kind of analysis.

The relationships shown in figs. 4 and 5 suggest that the use of vaccines of greater conversion efficiency would considerably reduce vaccine failures. Moreover, the linear relationship between dose and immunising effect is not incompatible with the possibility that the effects are irreversible. If this is so, it would seem that long-term immunity can be induced by a single adequate antigenic stimulus.

ANTIGENIC MASS

In immunisation with a formalin-treated virus vaccine, the use of multiple injections is based partly on the knowledge that high levels of antibody can be induced by a smaller dose of antigen if that dose is divided instead of being given on a single occasion. As shown in fig. 6, using reference vaccine "A" in man, when two doses were given, only about half as much antigen was required,

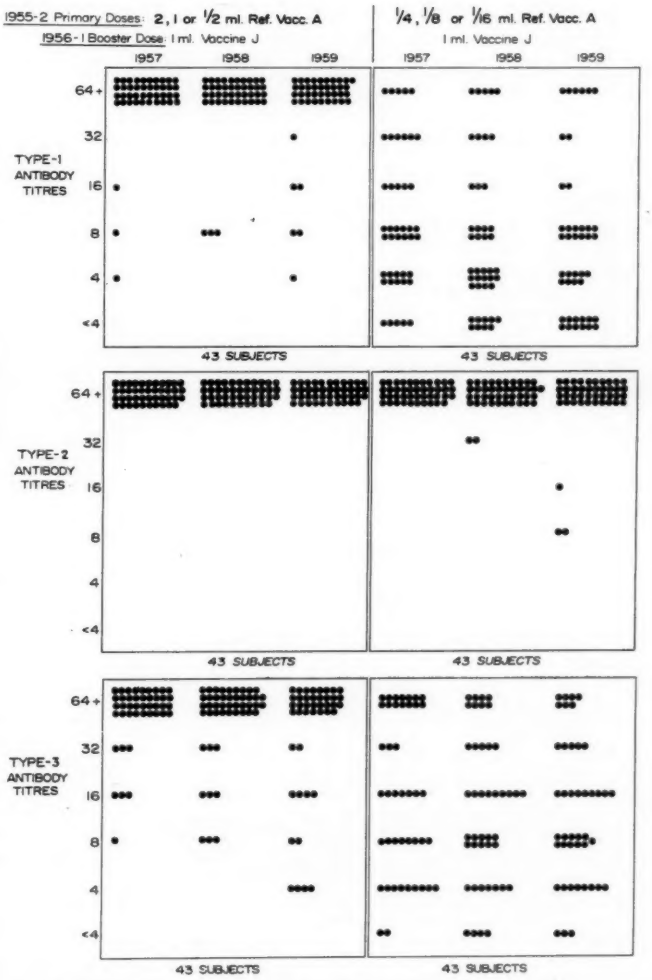

1955-2 Primary Doses: 2, 1 or 1/2 ml. Ref. Vacc. A
1956-1 Booster Dose: 1 ml. Vaccine J
1/4, 1/8 or 1/16 ml. Ref. Vacc. A
1 ml. Vaccine J
1957 1958 1959
TYPE-1 ANTIBODY TITRES
TYPE-2 ANTIBODY TITRES
TYPE-3 ANTIBODY TITRES
43 SUBJECTS

Fig. 7—Types 1, 2, and 3 antibody titres up to 3 years after booster dose.

to reach an equivalent antibody level, as was required when a single dose was given. When a third dose, which was uniform for all six groups, was postponed until one year later, substantial increases in antibody levels occurred —far beyond that induced by a single dose of a much larger amount of antigen. While the striking effect of a third dose given one year later is as shown in fig. 6, it was found that a third dose given only two weeks after the second induced only slight changes in titre, which shows the need for adequate spacing of doses if the maximal response is to be obtained from small amounts of antigen.

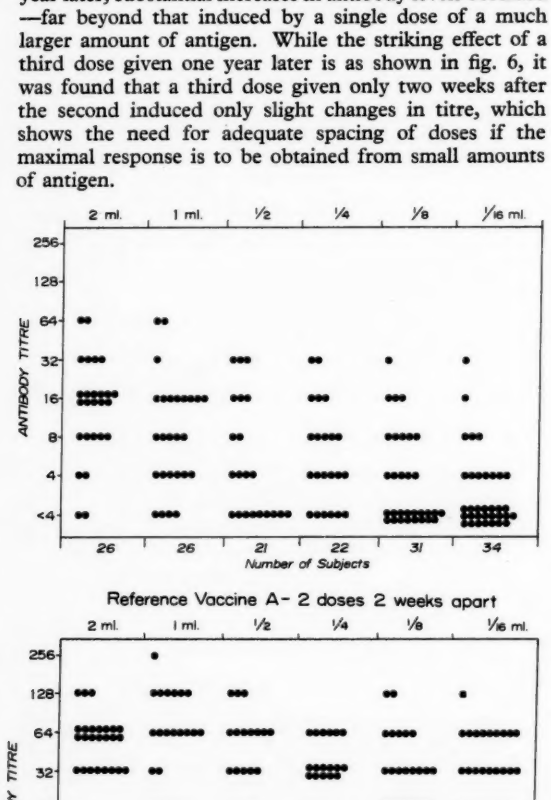


Fig. 8—Types 1, 2, and 3 antibody titres 1 year after primary vaccination.

The top, middle, and bottom portions of the figure refer to data for types 1, 2, and 3 respectively.

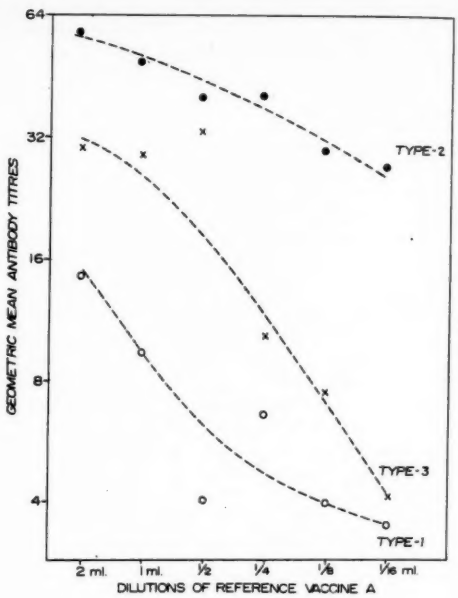


Fig. 9—Dosage response effect. Geometric-mean antibody titres 1 year after primary vaccination (two doses, 2 weeks apart).

The high antibody levels developed after the booster dose are not required for induction of the immune state; effective immunity to paralysis can be induced by a primary antigenic stimulus.

Persistence of Immunity

ANTIGENIC MASS

Antigenic mass affects not only the level of antibody developed initially but also the persistence of demonstrable antibody. At one year and two years after a booster dose, higher levels of antibody, and a higher proportion with demonstrable antibody, are found in groups given a larger dose for primary immunisation (Salk 1958). In the experiment illustrated in figs. 6 and 7, the levels of antibody, and the proportion with demonstrable antibody, were higher in those who had been given the three larger doses of vaccine than in those given the three smaller doses. Since the booster doses were the same, the level of antibody persisting was evidently related to the mass antigen employed for the initial injections. It appears from these data (fig. 7) that successful induction of a state wherein antibody formation tends to persist, and the level at which this is maintained, are linked to the amount of antigen in the initial dose of vaccine.

If the level of antibody one year after the booster dose were found to be related to the subsequent level of persistence, this might also be true of the level of antibody one year after primary immunisation. Fig. 8 shows, for each of the three types, the distribution of antibody levels one year after two doses, given two weeks apart, of different dilutions of reference vaccine " A ". Clearly the frequency with which antibody is present one year after primary vaccination is determined by the mass of antigen employed. Moreover, as is to be expected, the mean level of antibody is correspondingly influenced.

When geometric-mean antibody levels for each type are plotted (fig. 9) in relation to quantity of reference vaccine " A " used for immunisation, the results arrange

themselves at different levels and along lines of different shape. The meaning of the different levels and lines of different shape could be that each was but a segment of a more extensive curve, and not part of a straight line describing a simple function. The reasonableness of this explanation became apparent when the lines were rearranged by horizontal shifting so as to touch at essentially overlapping points. When this was done (fig. 10) the points approximated a single sigmoid curve. This suggests that if the titration series could have been extended to the same limits for each type, a similar sigmoid curve would have described the dosage-response effect in each instance. The meaning of the shape of this curve will be discussed at a later time.

The quantitative relationship shown in fig. 10 is of particular interest at present since it suggests the nature and extent of decreases or increases in antigen content, in relation to reference vaccine " A ", that may be permitted, or may be required, to achieve an equally high level of performance for all three types. By plotting (fig. 11) the percentage of persons with antibody titres of 1/4 or more one year after vaccination, in relation to the abscissa used in fig. 10, it becomes apparent that there is a critical antigen content below which this percentage falls sharply.

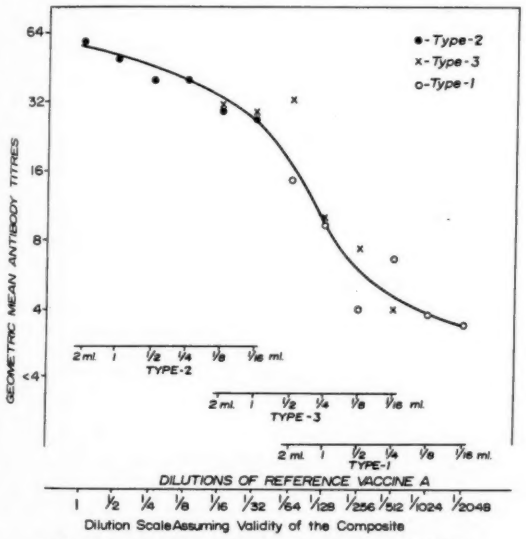


Fig. 10—Composite curve for dosage-response effect.
Adjusted for differences in mass or specific activity of three components of reference vaccine " A ".

If the object of immunisation is to achieve a level of antibody that persists for at least a year after primary vaccination, the relationships shown in fig. 11 (left-hand curve) indicate the approximate relative amounts of the respective antigens contained in reference vaccine " A " that may be expected to attain this objective, when two doses are given two weeks apart. Fig. 11 also shows (right-hand curve), for comparison, the one-dose response measured at two weeks.

Although levels of potency based upon positive serological criteria would be higher than levels based upon paralysis-prevention criteria, a good estimate of the requirements for optimal potency

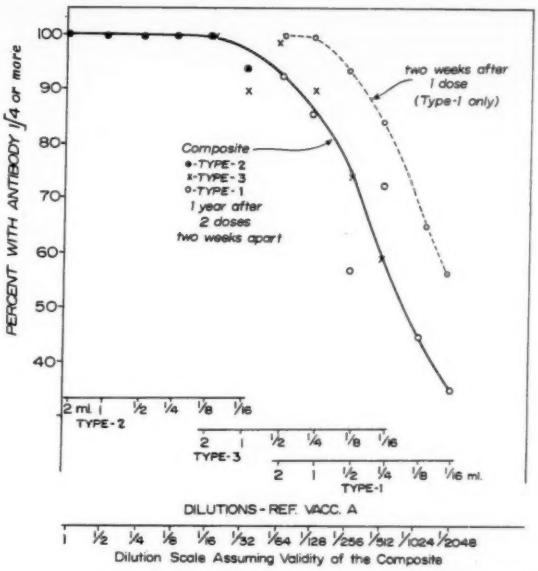


Fig. 11—Composite curve showing percent with antibody at level of 1/4 or more.
Derived from dosage response data adjusted for differences in mass or specific activity of three components of reference vaccine " A ".

can be deduced, in part, from the relationships revealed by the data presented in fig. 4. The assumption may be made that the immunising effect for type 1 should be increased to the extent desired beyond that of approximating a 50% effect with a single dose. The amount of antigen needed for such an increase may be deduced from the relationships shown in fig. 11, which indicates that the amount of type-1 antigen contained in one dose of 1/2 dilution of reference vaccine " A " was sufficient to induce, in all subjects, titres of 1/4 or more after one dose, and that, after a two-dose primary vaccination, about four times this amount was necessary to induce a demonstrably persistent level of antibody for one year. From fig. 7 it seems that when primary vaccination

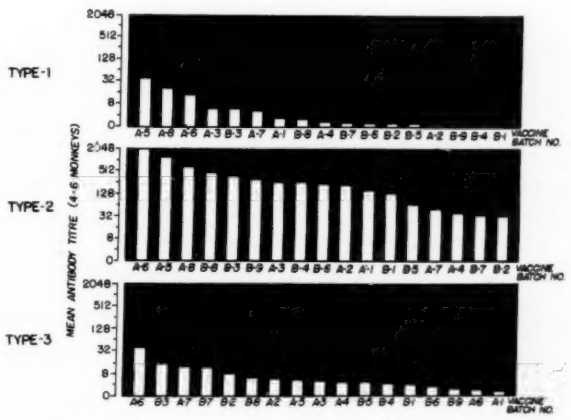

MEAN ANTIBODY TITRE (4-6 MONKEYS)
TYPE-1
TYPE-2
TYPE-3
2048
512
128
32
8
0
A-5 A-6 A-8 A-3 B-3 A-7 A-1 B-8 A-4 B-7 B-6 B-2 B-5 A-2 B-9 B-4 B-1
A-6 A-5 A-8 B-8 B-3 B-9 A-3 B-4 B-6 A-2 A-1 B-1 B-5 A-7 A-4 B-7 B-2
A-6 B-3 A-7 B-7 B-2 B-8 A-2 A-5 A-3 A-4 B-5 B-4 B-1 B-6 B-9 A-8 A-1
VACCINE BATCH NO.

Fig. 12—Mean titre of antibody in cynomolgus monkeys 4 weeks after a single administration of 10 ml. of 18 different batches of poliomyelitis vaccine divided among four intramuscular sites. (From Salk et al. 1955.)

consisted of two doses of a 1/2 dilution of reference vaccine "A" given two weeks apart, followed by a third dose a year later, antibody was still demonstrable for at least another three years.

If the relationships thus revealed in terms of antibody are true also of immunity to paralysis, it would seem that an antigen content increased eight-fold to ten-fold over the average of the recent past is in the range of the minimum required for optimal effectiveness for type 1. This estimate is in the range found by Barnett and Baron (1960) to compensate for deficiencies in potency. They, and Dane et al. (1960), recommend that in the face of epidemics, 10 ml. of the generally available vaccine should be used to obtain prompt and more uniform effects—comparable to those induced by 1 ml. of reference vaccine "A".

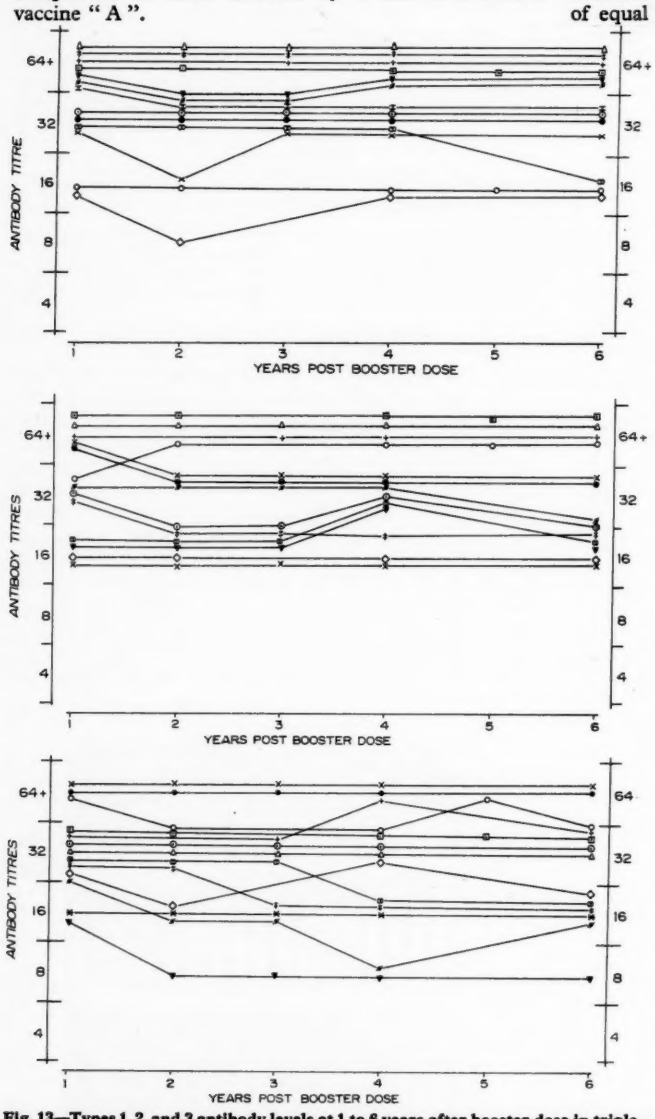


Fig. 13—Types 1, 2, and 3 antibody levels at 1 to 6 years after booster dose in triple-negative children.

The top, middle, and bottom portions of the figure refer to data for types 1, 2, and 3 respectively.

Two doses 2 weeks apart; third dose 7 months to 1 year later.

Although these analyses indicate an increase in the average amount of type-1 antigen, the problem may be more simply one of assuring stability and restricting acceptability only to lots of vaccine of such potency as can be expected to perform as intended. These analyses also suggest that the amount of type-2 antigen may be reduced. Specifications for type 3 should be determined, using as a guide field experience for type 1 and the immunological experience with the type-3 component of reference-vaccine "A".

ANTIGENIC CAPACITY OF DIFFERENT STRAINS

Apart from quantity, account must be taken of the intrinsic capacity of the antigen to induce an immune reaction. Though reference vaccine "A" was comprised of equal parts of culture fluid containing virus of each type, converted to vaccine in essentially the same manner, the response to type 2 (MEF-1) differs from the response to the other two components (figs. 7, 9, and 10). This difference is unlikely to be due only to differences in quantity or mass of antigen: that some qualitative difference must exist has long been appreciated (Salk et al. 1953, Salk et al. 1955). Because of the potential importance of the difference in antigenic capacity among these strains (Mahoney, MEF-1, and Saukett), an investigation is under way exploiting the earlier observed difference (Salk et al. 1955) in one-dose response in monkeys (fig. 12). Although multiple injections obliterate the marked one-dose difference by enhancement of response to all three strains, the possibility of differences in degree and persistence of immunologic response to different strains of virus is interesting both theoretically and practically.

PROJECTION OF ANTIBODY PERSISTENCE

Fig. 7 illustrated the degree of persistence of antibody during the three years following the last dose of vaccine. The trends over a period of about six years, following a booster dose given seven to twelve months after primary immunisation, are shown in fig. 13. These data show that the level of demonstrable antibody a year after the booster dose is a guide to the level during the next six years. The individuals comprising the group shown in fig. 13 were among those in whom good response occurred. They appear to follow the pattern of the group given the larger dose of reference vaccine "A" for primary immunisation (fig. 7). The persistence of antibody after primary immunisation (fig. 14) is similar to that following the booster dose. Instances of a rise in antibody titre for one type (indicative of natural infection during the period of observation), or for two or three types (suggesting vaccination), have been excluded from the foregoing analyses. The present observations bear on the unresolved question whether persistence of antibody to a virus disease requires either the continued presence of living virus or repeated reinfections. They suggest that antibody can persist merely as a result of an initially adequate antigenic stimulus.

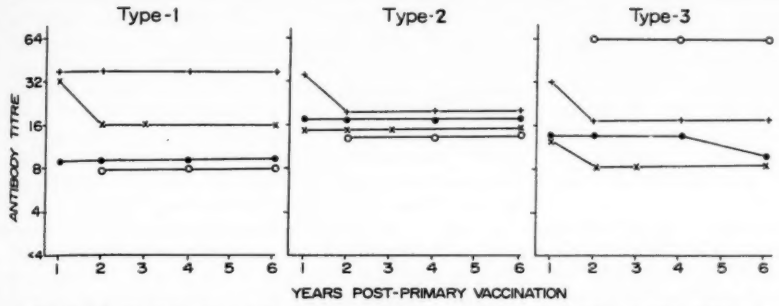


Fig. 14—Antibody levels at 1–6 years after primary vaccination in triple-negative children. Three doses 2 weeks apart. (Field trial vaccine, 1954.)

From figs. 13 and 14 as well as fig. 7, it seems that for predicting the decline in antibody level with time, a line connecting the levels one year and two years after the booster dose will be more informative than the line connecting the levels two weeks after primary vaccination and one year after the booster dose. The pattern of the two different projections can be seen from fig. 15, which shows antibody levels over a seven-year period in a child given one primary and one booster dose seven months apart. A similar pattern of persistence in the early and later periods has been observed after primary immunisation.

Whether a persistently demonstrable level of antibody is essential for persistently effective immunity to paralysis is not certain, since there is reason to believe that immunity to paralysis continues in those rendered immunologically hyperreactive by contact with antigen, and in whom antibody may no longer be detectable by usual methods (Salk 1956b). But there can be no doubt that for maintaining a readily demonstrable level of antibody the intensity of the initial antigenic stimulus is important.

Is Induced Immunity Reversible?

The idea suggested earlier that a single dose of antigen may have an irreversible immunising effect looks more plausible in the light of the evidence presented above.

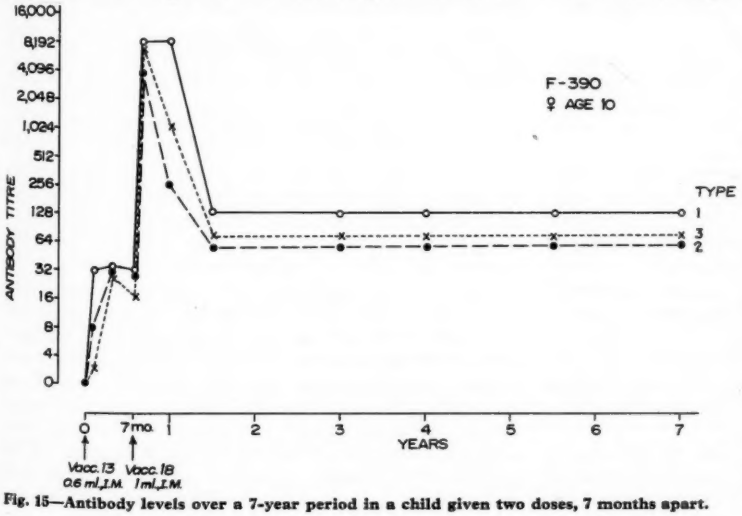


Fig. 15—Antibody levels over a 7-year period in a child given two doses, 7 months apart.

The importance of this idea, for non-infectious vaccines in general, warrants examination of the dynamics that might be involved.

Ordinarily vaccination is regarded as adding to the host something that was not there before—i.e., a state of immunity. But there is another possible way of looking upon this phenomenon—an alternative explanation of the effects of vaccination—namely, that it inactivates susceptibility. This may lead to another way of thinking about the dynamics of immunisation.

If the hypothesis that long-term immunity can be induced by a single antigenic stimulus is correct, we might then speak not only of vaccination inactivating susceptibility but also perhaps of an irreversible inactivation of susceptibility comparable to the inactivation of a virus. In line with this reasoning, the linear relationship in fig. 1 brings to mind the dynamics of biological systems in which irreversible inactivation takes place. Such linear relationships usually imply that the inactivation of the measured property is a consequence of some single or final critical event. In this instance, the relationships in fig. 4 suggest that the likelihood of the critical event is influenced by the mass of antigen employed. The nature of the critical event can be suggested only in the broadest terms, but it can be imagined as the conversion of a sufficient number of antibody-forming cells to a state in which, on exposure to natural infection, they will produce enough antibody to prevent paralysis.

The slope of the line describing the rate of inactivation of susceptibility becomes steeper with increasing concentrations of antigen in the vaccine (fig. 4). This would be analogous to the increased rate at which virus is inactivated when

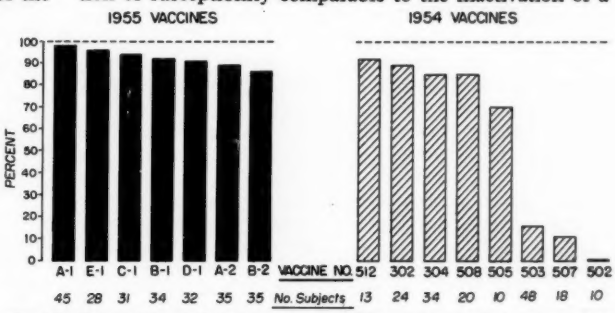


Fig. 16—Percentage of children with antibody response type 1 on the 14th day after first dose of vaccine. (From Salk 1955.)
No prior demonstrable antibody to any type.

one increases the concentration of formaldehyde or raises the temperature. Just as a 1/8000 or a 1/16,000 concentration of formalin at 37°C would take an inordinately long time to inactivate poliovirus for vaccine preparation, so a vaccine with a concentration of antigen able to inactivate (by a single dose) the susceptibility of only 50–60% of subjects may take an inordinately large number of injections and an inordinately long time to have the desired effect.

In using a formalin-treated virus antigen, therefore, the aim should be a preparation that is fully effective in a single dose. Whether this is to be accomplished by sufficient concentration of the antigen or by the use of an adjuvant is a detail to be decided on other grounds. The point of importance is that whatever increases the frequency of effectiveness will simultaneously enhance the durability of effect.

Discussion

When the value of a preventive measure is demonstrated, the need to apply it soon destroys the chances of varying, in a controlled way, the critical factors on which more precise knowledge may be required. For this reason, it was not expected that much further quantitative information on the efficacy of vaccination could be gathered beyond that derived from the Francis study (Francis et al. 1957). However, valuable information on the incidence of paralytic poliomyelitis in relation to the number of doses of vaccine was collected in the United States in 1959. This was possible because of the excellence of the poliomyelitis surveillance programme of the United States Public Health Service, and the cooperation it receives from various agencies and professions.

DYNAMICS OF IMMUNISATION

This 1959 experience provided an unusual opportunity for titrating vaccine effectiveness according to the number of doses, using immunity to paralysis rather than antibody level as the endpoint. The degree of protection to be expected after successive doses proves to be related to the protection conferred by a single dose. The 50% paralysis-protection endpoint for one dose has provided a basis for estimating the nature, direction, and extent of the changes required to approximate full effectiveness through adjustment of vaccine potency.

It has been shown that when adequate antigenic stimulation is induced initially, antibody persists for at least six years; and even if immunity to paralysis continues after antibody has declined to non-measurable levels (Salk 1956b), it seems much more likely to continue where demonstrable antibody has persisted for a year or more than where it persisted only a few weeks or months. Long-term presence of antibody has been induced by primary immunisation, and this encourages the hope that a single dose, if suitably adjusted in potency, may regularly have long-term and possibly even permanent effects.

A one-dose procedure is the goal. Meanwhile, however, it should be possible at least to fulfil the original intention of giving full protection by means of two primary doses. The present three-or-four-dose procedure still leaves a small but measurable residue of susceptibles but this remnant of the consequences of earlier imperfections could be dissolved by a single dose of vaccine of optimal potency.

When a two-dose primary vaccination procedure was first proposed (Salk 1955), it was assumed that vaccines would approximate the antigenic potency of the 1954 field trial material prior to the deteriorating effect of merthiolate. The first seven batches of vaccine commercially prepared in 1955 are compared in fig. 16 (Salk 1955) with representative lots of field-trial vaccine; it shows that after a single dose, at least 85% of those vaccinated with the 1955 material developed an antibody titre of 1/4 or more whereas potency of some lots of the 1954 material, which had been impaired by merthiolate action, were of lesser effectiveness.

It was to be expected that two doses of vaccines of such potency would have closely approximated full effectiveness, and that a third dose, seven months to a year later, would induce the high levels associated with the booster phenomena. These expectations were fulfilled (Salk 1956a). However, a survey made in 1957 showed that the vaccines then in general use were less effective (Salk 1959a).

The 1959 experience (fig. 4) suggests that one dose protected an average of about 50%, three doses protected about 92%, and four doses protected about 96%. The decrease in efficiency between 1955 and 1959 can be explained as due to use of a mixture of vaccines of high and low potency (fig. 16). From data in fig. 11 it appears that the range of potencies of vaccine manufactured in the United States, with respect to types 1 and 3, must have been in the critical range between poor and satisfactory, as judged by their effectiveness using the number of injections originally intended. By a shift to higher levels of potency, effectiveness with greater consistency can be expected, and a higher proportion of vaccinated subjects will show persistence of demonstrable antibody.

PROSPECTS

The fact that vaccine potency was high in 1955, declined for a time, and is now increasing again (Murray 1960), indicates that levels of performance can be raised when the need is clearly established. The five years' experience accumulated since the 1954 field trial has provided better understanding of what needs to be done to approximate perfection in the use of a formalin-treated virus vaccine against poliomyelitis. Moreover, how this can be done has become much clearer.

For example, the uncertainty of effect in young infants attributable to a variable amount of maternal antibody is greatest with vaccines of borderline potency, and can be overcome by more potent antigens. If the vaccine used was of one-dose effectiveness, such uncertainty could be further reduced by the simple expedient of giving a second dose after 6 months of age. Alternatively, mothers can themselves be immunised, and the immunisation of the child can be left until he is 6 months old.

Another approach to the problem posed by the inhibiting action of maternal antibody was suggested by an observation made earlier that antigen contained in a water-in-oil emulsion appears to be protected from the neutralising effect of antibody. The use of such an emulsion can be expected (*a*) to enhance antigenicity, (*b*) to require the use of less antigen, and (*c*) to permit admixture of several viral and other compatible antigens into a multivalent vaccine to be given to all new members of the population early in life. Whether mineral-oil adjuvants will ultimately be used depends on many factors still under study. The likelihood that, in time, many different purified and concentrated antigens will be available, considerably extends the possibility of their manipulation to provide the most practicable procedure.

The method developed by Charney et al. (1957) for concentrating poliovirus shows the possibility of preparing vaccine of any desired level of potency, and vaccine preparation can be simplified in other ways. The possibilities include selection or development of strains of higher specific antigenic activity, and the use of continuously propagating cells for cultivation of virus. These possibilities justify the expectation that the objectives reached for poliomyelitis will be extended to include antigens for a number of other viral diseases.

With vaccines of single-dose effectiveness, not only will almost all vaccinated people be protected promptly and persistently, but the spread of virus in the population will be dampened more efficiently, and even totally suppressed. Prevention of spread of virus from the intestinal canal to the pharynx, by antibody in the bloodstream, would protect the community by reducing the pharyngeal reservoir (Salk 1959b) which in some parts of the world seems to be a more common source of spread than fæcal contamination. There is reason to think that, where vaccination has been widespread, type-2 virus may already have been substantially suppressed (Salk 1959a). If this proves to be so, it may be due to the greater antigenic effectiveness of the vaccine for this type, and a similar herd effect may be expected for types 1 and 3 when immune conversion for these types reaches the type-2 level.

The statement sometimes made (Chumakov 1960), that 20 or 30% of the population are not protected by the formalin-treated virus vaccines at present available, does not seem to be in keeping with the observations reported or cited here. If some people are totally non-responsive, they must be very few—i.e., they have escaped notice in observations on more than 10,000 individuals. There are, however, some who react more to one type than to the others. These rare individuals are being accumulated, and in time more will be known about them and their frequency.

Concluding Remarks

These studies on immunisation with formalin-treated virus antigens have had as their purpose, in part, the establishment of the parameters within which protection against poliomyelitis paralysis could be induced with a high degree of certainty. The work was begun on the assumption that two or more doses of vaccine would always be required, but experience now suggests that lasting protection against the disease should be attainable with a single dose.

The view that a formalin-treated virus vaccine for poliomyelitis was merely a stage awaiting the development of a live virus vaccine seems to have underestimated the potentialities of non-infectious viral antigens.

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REFERENCES

Barnett, E. V., Baron, S. (1960) *Amer. J. Hyg.* **71**, 59.
Charney, J., Fisher, W. P., Machlowitz, R. A. (1957) *Proc. Soc. exp. Biol., N.Y.* **96**, 601.
Chumakov, M. P. (1960) *Acad. Med. Sci.* of U.S.S.R., Institute for Poliomyelitis Research, report no. 2.
Dane, D. S., Dick, G. W. A., McAlister, J. J., Nelson, R. T. (1960) *Lancet*, i, 845.
Francis, T., Jr., Napier, J. A., Voight, R. B., Hemphill, F. M., Wenner, H. A., Korns, R. F., Boisen, M., Tolchinsky, E., Diamond, E. L. (1957) Evaluation of the 1954 Field Trial of Poliomyelitis Vaccine. University of Michigan.
Langmuir, A. D. (1960) Report to Fifth International Poliomyelitis Conference, Copenhagen, July 27, 1960.
Murray, R. (1960) *ibid.*
Olin, G. (1960) *ibid.*

References continued at foot of next column

A TRIAL OF CONTINUOUS WINTER CHEMOTHERAPY IN CHRONIC BRONCHITIS

RONALD B. PRIDIE
M.B. Lond.
LATELY MEDICAL REGISTRAR

NAOMI DATTA
M.D. Lond., Dip. Bact.
ASSISTANT LECTURER IN BACTERIOLOGY

D. G. MASSEY
M.D. Toronto
MEDICAL REGISTRAR

GRAHAM W. POOLE
M.B. Birm., M.R.C.P.
ASSISTANT PHYSICIAN

J. SCHNEEWEISS
M.B. Sydney
MEDICAL REGISTRAR

PETER STRADLING
M.D. Lond., M.R.C.P.
PHYSICIAN AND LECTURER

From the Hammersmith Chest Clinic and Postgraduate Medical School of London, W.12

THE death-rate from chronic bronchitis far exceeds that from cancer of the lung, and it is some five times that from road accidents (Ministry of Health 1958).

As the serious plight of patients with chronic bronchitis is increasingly recognised, the problem of relief is receiving widespread attention. Waller and Lawther (1957) and Lawther (1958) showed that the wellbeing of chronic bronchitics varies inversely with the smoke concentration of the atmosphere; Oswald and Medvei (1955), and many others (Edwards et al. 1959, Flick and Paton 1959, Higgins 1959) have shown a relation between smoking and chronic bronchitis. Because these factors are beyond the direct control of the physician many workers have used chemotherapy in efforts to reduce the infection associated with the disease, and drugs have been given during exacerbations only or continuously during the winter months:

Elmes et al. (1957), Moyes and Kalinowski (1959), and Berry et al. (1960) showed, in controlled trials, that treatment with oxytetracycline or tetracycline, 1 g. daily, given only during exacerbations, might shorten the exacerbation and reduce considerably the time lost from work.

Helm et al. (1954, 1956) treated a small number of patients with continuous oxytetracycline (1–3 g. daily), and reported improvement. May and Oswald (1956) made a similar claim for daily doses of tetracycline or oxytetracycline of 0·25–1 g.

Controlled trials of continuous daily chemotherapy have been undertaken with chlortetracycline 0·5 g. in 30 patients (McVay and Sprunt 1953); using various doses of oxytetracycline or ' Sulphatriad ' in 53 patients (Edwards et al. 1957, Edwards and Fear 1958); using tetracycline 0·75 g. in 90 patients (Moyes and Kershaw 1957); using tetracycline 0·5 g. in 51 patients (Buchanan et al. 1958); using tetracycline 0·75 g. in 25 patients (Moyes and Kalinowski 1959); and with a tetracycline-oleandomycin preparation 1 g. in 23 patients, or oxytetracycline 1 g. in 75 patients (Murdoch et al. 1959). All claimed benefit from the tetracycline group of drugs. In the

DR. SALK: REFERENCES—*continued*

Poliomyelitis Surveillance Unit, Communicable Disease Center, Public Health Service, United States Department of Health, Education, and Welfare (1960). Poliomyelitis Surveillance Report no. 194, March 11, 1960.
Prinzie, A., Lamy, M., de Maeyer, E., de Somer, P. (1960) *Rev. med. Louvain*, **24**, 202.
Salk, J. E. (1955) *Amer. J. publ. Hlth*, **45**, 575.
— (1956a) *J. Amer. med. Ass.* **162**, 1451.
— (1956b) *Trans. Ass. Amer. Physcns*, **69**, 105.
— (1958) *J. Amer. med. Ass.* **167**, 1.
— (1959a) *Roy. Soc. Hlth J.* **79**, 310.
— (1959b) *Ann. intern. Med.* **50**, 843.
— Contakos, M., Laurent, A. M., Sorensen, M., Rapalski, A. J., Simmons, I. H., Sandberg, H. (1953) *J. Amer. med. Ass.* **151**, 1169.
— Lewis, L. J., Bennett, B. L., Ward, E. N., Krech, U., Youngner, J. S., Bazeley, P. L. (1955) *Amer. J. publ. Hlth*, **45**, 151.

recent trial of chemotherapy in chronic bronchitis conducted by the British Tuberculosis Association (1960) both tetracycline (0·5 g. daily) and phenoxymethylpenicillin (penicillin V, 624 mg. daily) halved the length of exacerbations but did not affect their frequency.

The bacteriology of the sputum of chronic bronchitics has been studied by a number of workers, including Mulder et al. (1952), Stuart-Harris et al. (1953), and May (1953, 1954). All found that *Streptococcus pneumoniæ* and *Hæmophilus influenzæ* were the most significant organisms, and they pointed out that penicillin is highly effective against *Str. pneumoniæ* but less so against *H. influenzæ*, whereas sulphonamides, which are effective against *Str. pneumoniæ*, have little effect on *H. influenzæ*.

To test further the validity of the published conclusions on long-continued chemotherapy, and to give penicillin with sulphonamide a practical trial, we undertook a double-blind controlled experiment to compare oxytetracycline, a penicillin-sulphonamide combination, and a placebo. We thought it possible that the penicillin-sulphonamide preparation, as well as being cheaper (£10 per patient for the doses used in this trial compared with £33 for oxytetracycline), might produce fewer side-effects, and thus, if similarly effective, might prove more suitable.

Method

The trial was held during twenty-four weeks, from Nov. 2, 1958, and only adult chronic bronchitics with some exertional dyspnœa were admitted. During the previous three winters each had had at least one disabling respiratory illness with two months' cough and sputum. Patients with active tuberculosis, proved bronchiectasis, carcinoma of the bronchus, or other chest disease were excluded.

The oxytetracycline dosage (0·5 g. daily) was the minimum found effective in previous controlled trials (McVay and Sprunt 1953, Buchanan et al. 1958). The treatment chosen for comparison was potassium phenoxymethylpenicillin 500 mg. with sulphadimidine 2 g., in combined tablets daily.

151 patients were admitted to the trial and divided into six subgroups by a method based on random sampling numbers. Two subgroups were given penicillin-sulphonamide tablets and one subgroup had dummies of similar appearance; two subgroups received oxytetracycline tablets and the last subgroup had similar dummies. Both placebos contained lactose. The division into six subgroups was necessary because the tablets looked different; by combining appropriate subgroups, we obtained a placebo group similar in size to each treatment group. These three groups comprised 51 patients having placebos, 51 having oxytetracycline, and 49 having penicillin-sulphonamide.

At a preliminary interview, the trial was carefully explained to each patient; the work status was recorded, a chest radiograph was taken, and the grade of dyspnœa was assessed. The vital capacity and the forced expiratory volume in the first second ($F.E.V._1$) were estimated. These tests were repeated after three months and at the end of the trial.

Each fortnight every patient was given a diary card on which to record his daily condition by a code letter: A = better than usual, B = same as usual, C = worse than usual, D = much worse than usual.

All the sputum produced in a period of twenty-four hours was collected from each patient before the start of the trial and every two weeks thereafter. The volume was measured each time and the macroscopic appearance graded as watery, mucoid, or purulent. From the specimens provided initially, after a month, and at the end of the trial, counts were made both of total bacterial content and of individual organisms.

TABLE I—EXCLUSIONS FROM ANALYSIS

Exclusions	Placebo group	Oxytetracycline group	Penicillin-sulphonamide group
Complete:			
Toxic	0	3	4
Non-toxic	1	2	2
Partial:			
Toxic	0	0	3
Non-toxic	7	6	5
Total due to toxicity	0	3	7
Total no. of exclusions	8	11	14

The patients were given postcards by which to notify the clinic of any respiratory illness, whereupon they were visited by a clinic doctor. General practitioners were fully informed of the trial, and they were asked to discontinue the trial tablets during an exacerbation, and to give their customary treatment for acute bronchitis. Both they and the patients were asked to ensure that the trial tablets were resumed afterwards. All other usual supportive measures, such as bronchodilators, were continued as necessary throughout the trial.

Daily records of the smoke and sulphur-dioxide content of the atmosphere were obtained from meteorological centres in three adjacent boroughs.

Health visitors called fortnightly at the patients' homes to provide a coordinating influence on the trial and to encourage cooperation. They exchanged the diary cards and ensured their completion, collected the sputum specimens, and issued further supplies of tablets, and collected those unused. (We thought this would give some indication of whether the patients had taken their tablets conscientiously. Every fortnight patients were given a sixteen-day supply of tablets, and since it was the routine to return two days' tablets, we thought it likely that they would also unwittingly return any other tablets that should have been taken rather than throw them away.)

At the end of the trial each patient's opinion was asked on the value of the treatment prescribed.

Exclusions from the Analysis

Patients who failed to complete the first month of the trial were excluded entirely from the analysis (complete exclusion). Those withdrawn after one month were included in the analysis up to the time of their withdrawal (partial exclusion). The details are presented in table I.

12 patients were completely excluded—1 in the placebo group, 5 in the oxytetracycline group, and 6 in the penicillin-sulphonamide group. This was because of intolerance to the drug in 3 patients on oxytetracycline (diarrhœa in each case) and in 4 on penicillin-sulphonamide (1 rash, and 3 complaints of dizziness).

The partial exclusions totalled 21, and in only 3 cases was drug intolerance the cause. Factors such as lengthy admission to hospital or moving from the district were responsible for all

TABLE II—AGE AND SEX DISTRIBUTION (AFTER EXCLUSIONS)

Age (yr.) and sex	Placebo group	Oxytetracycline group	Penicillin-sulphonamide group
20–29	4	0	1
30–39	2	2	1
40–49	10	5	4
50–59	16	15	13
60–69	16	17	19
70+	2	7	5
All ages	50	46	43
All ages:			
Male	37	34	36
Female	13	12	7
50–69:			
Male	24	25	25
Female	8	7	7

the partial withdrawals in the placebo and oxytetracycline groups, and for 5 of those in the penicillin-sulphonamide group. The others were due to abdominal pain in 2 patients and to giddiness in 1.

Toxic reactions were more frequent in the penicillin-sulphonamide group than in the oxytetracycline group (7 to 3).

After exclusions there remain for analysis 50 patients in the placebo group, 46 having oxytetracycline, and 43 having penicillin-sulphonamide.

Despite randomisation rather more young people were found in the placebo group than in the two treatment groups (table II), perhaps explaining the apparent initial differences

TABLE III—CONDITION AT START OF TRIAL

—	All patients			Age 50–69		
	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide
Total patients ..	50	46	43	32	32	32
Sputum character:						
No sputum ..	2	2	0	1	2	0
Watery ..	8	9	8	6	7	6
Mucoid ..	13	9	10	8	7	8
Purulent ..	27	26	25	17	16	18
Sputum volume (ml. per 24 hr.):						
None ..	2	2	0	1	2	0
1–49 ..	38	26	32	23	17	24
50 and over	10	18	11	8	13	8
Average ..	33·2	45·3	38·7	38·1	42·8	37·4
Vital capacity (litres):						
Under 1·5 ..	2	5	4	2	2	3
1·5–2·49 ..	19	18	17	14	15	13
2·5–3·49 ..	23	20	16	16	13	11
3·5 and over	6	3	4	0	2	3
Average ..	2·70	2·38	2·39	2·45	2·38	2·41
F.E.V.$_1$ (litres):						
Under 1 ..	16	20	17	12	14	12
1–1·99 ..	20	24	17	17	17	14
2 and over ..	14	2	7	3	1	4
Average ..	1·44	1·08	1·21	1·19	1·08	1·24
Dyspnœa:						
Slight ..	20	13	15	10	9	12
Moderate ..	21	19	19	14	15	14
Marked ..	7	10	7	7	6	5
Very marked	2	3	2	1	1	1
Activity:						
Working ..	42	30	29	27	23	23
Not working	7	8	10	4	5	6
Housebound	1	6	2	1	4	1
Bedfast ..	0	0	0	0	0	0

The grade of dyspnœa for 1 patient and of activity for 2 patients on oxytetracycline were not available. For 2 patients on penicillin-sulphonamide no pulmonary ventilatory tests were done and the grade of activity was not available. All these patients were aged 50–69.

favouring the controls (table III). This discrepancy may be due partly to the bigger number and greater ages of the exclusions from the treatment groups. To evaluate this difference, the results for patients aged 50–69 were analysed separately. Between these ages the three groups were more clearly alike in all aspects of their condition on admission to the trial. Both sets of figures are presented, and their similarity suggests that conclusions drawn from the whole series are valid.

Results

Sputum

Table IV shows a similar reduction in sputum volumes in all three groups in the last two months of the trial (March and April), when the weather was improving. During the first four months, sputum volumes were reduced in the penicillin-sulphonamide group but not in the others. There was no significant difference in purulence (at the 5% level, as used throughout this study) between the three groups at any stage of the trial.

TABLE IV—MEAN SPUTUM VOLUMES (ml. PER 24 HR.)

Months after starting	All patients			Patients aged 50–69		
	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-culphon-amide
0 (October) ..	33·2	45·3	38·7	38·1	42·8	37·4
1 (November)	36·5	45·7	34·0	45·3	46·5	30·4
2 (December)	38·2	45·9	37·9	41·1	48·9	36·6
3 (January) ..	35·8	46·1	33·6	37·4	47·9	27·1
4 (February) ..	35·8	44·5	30·5	43·5	47·3	27·9
5 (March) ..	28·6	35·5	27·3	32·7	31·8	24·9
6 (April) ..	23·7	30·4	24·4	26·0	30·1	21·6

Ventilatory Function

Only changes of 10% or more from the initial values were considered of clinical significance in assessing ventilatory function by standard methods. Table V, compiled on this basis, reveals no significant difference between the groups, although the treated groups have a marginal advantage in relation to F.E.V.$_1$, which is less obvious in the 50–69 age-group.

Subjective Assessment

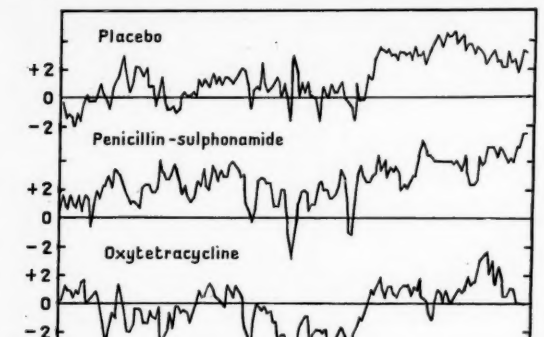
In the patients' subjective assessment at the end of the trial the proportion of patients noting benefit was similar in the placebo group and in the treatment groups. There is no significant difference between the three groups in the proportion showing reduction of dyspnœa or change in exercise level.

Figures derived from the daily recordings on the diary cards * show that the penicillin-sulphonamide group regularly did best, and the oxytetracycline group worst, although the difference reached statistical significance only in the second and fifth months. The degree of improvement was calculated by scoring "better than usual" as 1; "same as usual" as 0; "worse than usual" as −1; and "much worse than usual" as −2. The indices so obtained were plotted on the same time-scale as the average figures for smoke concentration (see figure). As the sulphur-dioxide figures ran parallel with those for smoke, they are not reproduced. The graphs for each

* Multigraphed tables of these figures may be had from *The Lancet*, 7, Adam Street, London, W.C.2.

TABLE V—CHANGES OF 10% OR MORE IN VENTILATORY FUNCTION

Ventilatory function	All patients			Patients aged 50–69		
	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide
Vital capacity (litres): October to January:						
Increase ..	6	5	6	5	3	4
No change	30	18	17	21	13	12
Decrease	10	20	11	4	16	9
Total ..	46	43	34	30	32	25
October to April:						
Increase ..	4	10	8	4	6	7
No change	25	17	14	16	13	9
Decrease	12	12	9	6	9	7
Total ..	41	39	31	26	28	23
F.E.V.$_1$ (litres): October to January:						
Increase ..	9	7	6	6	6	2
No change	20	16	13	14	11	9
Decrease	17	20	15	10	15	14
Total ..	46	43	34	30	32	25
October to April:						
Increase ..	6	9	7	3	7	4
No change	15	18	11	11	12	9
Decrease	20	12	13	12	9	10
Total ..	41	39	31	26	28	23



Degree of wellbeing of patients in each group, and smoke concentration in the atmosphere.

group all follow the same general pattern, and neither treatment altered their form. The penicillin-sulphonamide graph is at the highest level (most improvement), the placebo graph is intermediate, and that for oxytetracycline is lowest.

The trend in favour of penicillin-sulphonamide thus revealed may be important, although not statistically significant.

Exacerbations

Some of the patients listed in table III as " working " were housewives in whom it was impossible to determine, by means of the number of days off work, the duration of disability in each exacerbation. Accordingly comparison of such disability is only presented in relation to men (table VI). It is difficult to draw sound conclusions from the number of days off work per exacerbation because the trial tablets were stopped and the treatment was at the discretion of the general practitioners; but the patients in the treated groups were off work for a shorter time, on average, than those in the placebo group, although the differences were not statistically significant. Table VI also shows a slight difference in favour of the treated groups in relation to the number of exacerbations.

TABLE VI—EXACERBATIONS AND TIME OFF WORK IN MALE WORKERS

—	All ages			Aged 50–69		
	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide
Total patients	32	25	25	21	21	19
No. without exacerbations..	12	11	11	6	10	8
No.with exacerbations ..	20	14	14	15	11	11
No. of exacerbations ..	29	28	24	23	25	16
No. of days off work ..	430	271	309	351	261	249
Mean exacerbations per worker ..	0·9	1·1	1·0	1·1	1·2	1·2
Mean days off per worker..	13·4	10·8	12·4	17·0	12·4	13·1
Mean days off per exacerbation ..	14·8	9·7	12·9	15·3	10·4	15·6

Bacteriology

Bacteriological counts * were recorded in logarithmic form because of the wide range of individual numbers. No significant difference was shown between either of the treated groups and the control group in the total counts for any month. Despite this the numbers of *Str. pneumoniæ* were noticeably reduced in both treated groups, particularly after one month but also at six months, as compared with the placebo group. Whilst the total bacterial counts were not raised, the incidence of *Str. pneumoniæ* and *H. influenzæ* was higher in the more purulent sputa, confirming the work of May (1953). Only 2 patients harboured staphylococci in their sputum at the end of the trial; neither strain was resistant to the drugs used. The figures for *H. influenzæ* were so variable that no trend can be detected.

Tablet Taking

Only 10% of patients returned more than 10% of the tablets they should have taken. Judged by this alone, cooperation in tablet taking seemed satisfactory.

Discussion

This double-blind trial with 151 patients does not show clear benefit from long-continued daily administration of either oxytetracycline (0·5 g.) or potassium phenoxymethylpenicillin (500 mg.) with sulphadimidine (2 g.). Our findings, like those of the recent trial (1960) conducted by the British Tuberculosis Association (B.T.A.), do not confirm the substantial reduction in the *frequency* of exacerbations that McVay and Sprunt (1953) and Buchanan et al. (1958) claimed with chlortetracycline or tetracycline 0·5 g. daily. On the other hand, neither of our treated groups showed so much reduction in the *length* of exacerbations as was obtained with tetracycline and with penicillin in the B.T.A. trial (50%). A possible reason may be the different procedures followed during exacerbations; the B.T.A. patients continued their prophylactic tablets whilst those in our trial did not. Hence, the B.T.A. patients probably had larger doses of antibiotics during exacerbations and consequently may have responded more quickly.

As a reduction in sputum volume in the last two months of the trial was found in all groups, it was presumably independent of treatment and may have been due to the improving weather. The penicillin-sulphonamide group, however, showed a steady and significant reduction in sputum volume during the first four months; and this group also had felt better. Since these are the only two factors that stand out, the subjective improvement might be dependent upon the reduction in sputum volume. Whether *continuous* administration of drugs is necessary to achieve this effect requires further investigation.

In contrast to our findings a number of other workers have reported significant benefit from larger doses (0·75 g.–1·0 g.) of broadspectrum antibiotics. Thus the dosage of the drug given may well be an important factor in producing a benefit. Higher dosage, however, increases the cost and possibly the toxicity—factors which must be weighed against the possible benefits of giving long-continued chemotherapy to bronchitics generally.

A correlation was noted between the rise in the smoke and sulphur-dioxide concentrations of the atmosphere and subjective deterioration in the patients confirming the work of Waller and Lawther (1957). This was so in all three groups, suggesting a dominant adverse influence of

atmospheric pollution on patients with bronchitis, which is largely independent of chemotherapy.

Some exacerbations are probably precipitated by the weather alone. The therapeutic effect of the drug taken at the onset of such exacerbations may account for their shorter length rather than the effect of the drug being truly prophylactic. If this is true, early and vigorous chemotherapy during exacerbations would be more logical than continuous administration.

Conclusions

The penicillin-sulphonamide combination was superior to both oxytetracycline and the placebo in reducing sputum and increasing wellbeing of chronic bronchitics. Nevertheless continuous daily treatment with oxytetracycline 0·5 g. or with potassium phenoxymethylpenicillin 500 mg. and sulphadimidine 2·0 g. produced objective effects so modest that we cannot recommend either regime. The control of winter bronchitis may require either a larger daily dosage of chemotherapy continuously, or very early and vigorous chemotherapy for exacerbations.

Summary

151 patients with winter bronchitis took part in a double-blind controlled therapeutic trial using a placebo, oxytetracycline, or a penicillin-sulphonamide preparation.

Daily doses of either oxytetracycline 0·5 g. or potassium phenoxymethylpenicillin 500 mg. with sulphadimidine 2·0 g. was used. The penicillin-sulphonamide group showed modest reduction of sputum volume and subjective improvement. Both treatment regimes brought about a small reduction, not significant at the 5% level, in the length of exacerbations, and they also reduced the incidence and numbers of *Streptococcus pneumoniæ*, but not of *Hæmophilus influenzæ*. A strong correlation was noted between atmospheric pollution and subjective deterioration of the patients, and this was similar in all groups.

The findings suggest that neither therapeutic regime, at the continuous daily dosage here employed, can be recommended to control winter bronchitis.

We are grateful to Dr. C. M. Fletcher and Dr. Philip Hugh-Jones for helpful criticism and for allowing us to include some of their patients; to Dr. Ian Sutherland for statistical advice and help; to Miss B. J. Kinsley for the arduous statistical analysis of the results and for much constructive criticism; to Miss Kathleen Reade, Mrs. June Haas, Mrs. Mary Greenwood, and Miss Yvonne Newton, the health visitors, for their cooperation, without which the trial would have been impossible; to Mrs. Megan Wall for central co-ordination and collection of data; to Mrs. Eileen Till for invaluable secretarial assistance; to Pfizer Ltd., for the oxytetracycline ('Terramycin') and dummy tablets; to Eli Lilly & Co., Ltd., for the penicillin-sulphonamide preparation ('V-Cil-K Sulpha') with dummies, and for a generous grant to cover expenses; to the medical officers of health for the boroughs of Chiswick, Fulham, and Kensington for allowing us access to the figures relating to atmospheric pollution kindly supplied by the Warren Spring Laboratory, Department of Scientific and Industrial Research.

REFERENCES

Berry, D. G., Fry, J., Hindley, C. P., Hodson, J. M., Horder, E. J., Horder, J. P., Marien, E. A. W., Rea, J. N., Ryle, A., Curwen, M. P., Tomlinson, A. J. H. (1960) *Lancet*, i, 137.
British Tuberculosis Association (1960) *Brit. med. J.* i, 297.
Buchanan, J., Buchanan, W. W., Melrose, A. G., McGuiness, J. B., Price, A. U. (1958) *Lancet*, ii, 719.
Edwards, F., McKeown, T., Whitfield, A. G. W. (1959) *ibid.* i, 196.
Edwards, G., Buckley, A. R., Fear, E. C., Williamson, G. M., Zinnemann, K. (1957) *Brit. med. J.* ii, 259.
— Fear, E. C. (1958) *ibid.* ii, 1010.
Elmes, P. C., Fletcher, C. M., Dutton, A. A. C. (1957) *ibid.* ii, 1272.
Flick, A. L., Paton, R. R. (1959) *Arch. intern. Med.* **104**, 518.
Helm, W. H., May, J. R., Livingstone, J. L. (1954) *Lancet*, ii, 630.
— — — (1956) *ibid.* i, 775.
Higgins, I. T. T. (1959) *Brit. med. J.* i, 325.
Lawther, P. J. (1958) *Proc. R. Soc. Med.* **51**, 262.
McVay, L. V., Sprunt, D. H. (1953) *Arch. intern. med.* **92**, 833.

References continued at foot of next column

MIDDLE-MENINGEAL HÆMORRHAGE

THE GENERAL SURGEON AND THE NEUROSURGEON

J. R. GIBBS
M.B. Brist., F.R.C.S.E.
NEUROSURGEON TO THE SOUTH-EAST METROPOLITAN REGIONAL NEUROSURGICAL CENTRE, BROOK GENERAL HOSPITAL, LONDON, S.E.18

THERE are still too many deaths from extradural hæmorrhage. This article is intended firstly to review the clinical features which may help a general surgeon to make his plans, and secondly to contribute to the organisation and practice of surgical treatment which at present is often haphazard. Though a few cases of extradural hæmorrhage will always be lost because of extensive coincidental brain damage, the others could and should be saved. To achieve this end there must be (1) watchfulness by the hospitals accepting head injuries, (2) liaison between those hospitals and neurosurgical centres, and (3) well-planned surgery.

Diagnosis

The diagnostic features of extradural hæmorrhage are well known, and a fully developed syndrome with a typical history is usually referred for surgery. The case causing hesitation in calling for help is the atypical one, with delayed or deepening coma, equal pupils, no hemiparesis, and no visible fracture radiographically; but the pupils occasionally do not keep faith, and a fine crack fracture may be invisible with X-rays. The only constant feature, therefore, is *advancing coma*—whether delayed, interrupted, or progressive.

The possible presentations are:

1. Coma appears for the first time 15 minutes to 48 hours (rarely up to a week or more) after a head injury.
2. Coma is immediate after the injury, but is interrupted by the classical lucid interval.
3. Coma is immediate after the injury and becomes progressively deeper. These cases present the greatest difficulty in diagnosis, for the majority are due to cerebral laceration and in few is life further endangered by a collection of extradural blood-clot. More rarely still is subdural fluid blood present in significant quantity.

Assessment of Unconsciousness

To say that "the patient is comatose" conveys little to the clinician, but the statement that "the patient is comatose and responds to nothing but severely painful stimuli on any of his limbs" is useful. All the limbs must be tested because coma cannot be judged by pinching a limb unless one knows, by comparison with the others, that it is not paralysed. A superficial pinch, if necessary firm and prolonged, is a more reliable test than a pinprick. Any resultant bruises are of no consequence.

That slowing of the pulse-rate may signify rising intracranial pressure is common knowledge, but it is less well known that phasic respirations precede the classical

DR. PRIDIE & OTHERS: REFERENCES—*continued*

May, J. R. (1953) *Lancet*, ii, 899.
— (1954) *ibid.* ii, 839.
— Oswald, N. C. (1956) *ibid.* ii, 814.
Ministry of Health (1958) Annual report, part II. H.M. Stationery Office.
Moyes, E. N., Kershaw, R. A. (1957) *Lancet*, ii, 1187.
— Kalinowski, S. Z. (1959) *Tubercle, Lond.* **40**, 112.
Mulder, J., Goslings, W. R. O., Van der Plas, M. C., Lopes Cardozo, P. (1952) *Acta med. scand.* **143**, 32.
Murdoch, J. McC., Leckie, W. J. H., Downie, J., Swain, R. H. A., Gould, J. C. (1959) *Brit. med. J.* ii, 1277.
Oswald, N. C., Medvei, V. C. (1955) *Lancet*, ii, 843.
Stuart-Harris, C. H., Pownall, M., Scothorne, C. M., Franks, Z. (1953) *Quart. J. Med.* **22**, 121.
Walfer, R. E., Lawther, P. J. (1957) *Brit. med. J.* ii, 1473.

Cheyne-Stokes pattern, and often go unnoticed because the breathing is not watched for a minute at a time.

Sleep may be superimposed on pathological lethargy, and in such a case stimuli more violent than those expected to rouse a sleeping adult serve only to lighten the coma momentarily. Underlying drowsiness can only be revealed by efforts to keep the patient awake for 1 or 2 minutes. After a mild head injury a child, when left alone comfortably in bed, will often sleep so heavily that his state is mistaken for coma. A head injury is an exhausting business, and fatigue is necessarily enhanced by, perhaps, several examinations at intervals. It is admittedly difficult not to be anxious in such circumstances, and no neurosurgical unit would be critical of an appeal to transfer the child for observation.

The Restless Case

A restless, struggling, noisy, violent, and inaccessible patient may be judged unconscious or stuporose—with justification, for he is almost certainly unaware of what he is doing and of what is going on around him. But oligosyllabic labels such as " comatose and restless " are not adequate to describe this complicated and interesting state. The patient can only be described as restless, struggling, noisy, violent, and inaccessible. Such a state may be due simply to confusion and a distended bladder, and a determined effort at catheterisation may be rewarded with a quiet patient. Otherwise restlessness may betoken headache with rising intracranial pressure from extradural bleeding, and suspicion may be increased if restlessness gives way within an hour or 2 to comparatively motionless coma. For this reason sedatives should be avoided if possible, but if necessary intramuscular paraldehyde is the safest drug. The state of consciousness then being no longer a yardstick, the development of lateralising signs must be depended on in the diagnosis of extradural hæmorrhage. If the blood-pressure is raised at this stage contact should be made with a neurosurgical centre, for it seems that sometimes the blood-pressure may play leap-frog with rising intracranial tension.

Lateralising Signs

When the state of consciousness has been assessed and recorded, one should look for the well-known inequality of the pupils; boggy swelling beneath the temporal muscle due to extravasated blood; hemiparesis; and a fracture in the temporal squama. Any or all of these lateralising signs may be absent, but usually at least one of them indicates the side needing exploration.

Very occasionally the pupil on the side of the hæmorrhage may for a time become smaller than its fellow before enlarging. Typically the ipsilateral pupil becomes inactive to light and enlarges, and the contralateral pupil lags behind in undergoing the same changes. When both pupils are fully dilated and fixed it is usually too late for treatment, and the patient's life may not be saved by evacuation of the clot. When bleeding is brisk, the whole sequence of pupillary changes may take less than an hour; and the change from unilateral to bilateral dilatation happens only too often during the journey from the diagnosing hospital to a neurosurgical centre.

An enlarged pupil does not always signify uncal herniation due to raised intracranial pressure. A wound near the orbit may produce immediate traumatic midriasis, the third nerve itself may be torn, or the optic nerve may be damaged by distortion or contusion (confirmation of this being possible only when the patient becomes sufficiently conscious for blindness to be recognised).

Hemiparesis is almost always contralateral to the blood-clot. If the patient is first seen in the late stages of deep coma hemiparesis may be impossible to recognise, and for this reason all observers should record the reaction to pain of each limb early in the illness while the patient can still respond.

A decerebrate attitude may affect the limbs on one or both sides; or there may be decerebrate seizures, usually in the form of tonic inversion of the limbs with or without paroxysmal hyperpnœa or opisthotonus. These are danger signs and treatment must be immediate.

Epilepsy after a head injury implies cerebral damage rather than compression by bleeding. As a diagnostic aid it is not helpful, and if unilateral it cannot be depended upon to indicate the side of the extradural hæmorrhage.

Surgical Treatment

The treatment of middle meningeal hæmorrhage should be in two stages—the immediate and the definitive.

THE IMMEDIATE OPERATION

This must of necessity sometimes be the business of the general surgeon, for death may result from extradural hæmorrhage within 3 hours of injury to the head. It involves making a burr-hole in the skull to release blood-clot under pressure, and suturing the scalp. If the definitive operation of craniotomy is not to follow immediately, it is best to elevate the depressed dura by hitching it to the scalp with a special needle, as described later. This is a simple operation, and it is extraordinary how even experienced surgeons will hesitate to do what is, after all, a great deal easier than an appendicectomy or tracheostomy.

Conditions have changed remarkably in the past 25 years. In 1935 Symonds and Jefferson, discussing the treatment of extradural hæmorrhage by evacuation of clot and suppression of bleeding points through an enlarged burr-hole, warned the general practitioner that he might find himself obliged to operate to save life. They wrote: " Whether the General Practitioner will attempt the operation will naturally depend upon local and personal considerations which are outside the scope of this article. If the progress of symptoms is rapid from hour to hour time is of the first importance, but when the development is measurable in terms of days there is usually opportunity for a carefully planned operation, and there is much to be gained from the services of a surgeon accustomed to the modern technique of cerebral surgery . . . but in the case of dire emergency, and this may arise, the practitioner must operate and make the best of it." It may be added that the emergency, seemingly obedient to the quickened pace of living, nowadays rarely takes days to develop, and sometimes minutes count rather than hours. Adams McConnell (1957), in a letter to *The Lancet* regarding extradural hæmorrhage, said: " Many fruitless journeys into the country have convinced me that the local surgeon must assume responsibility for such cases."

Technique

General anæsthesia is neither necessary nor desirable. In very urgent cases time should not be wasted taking radiographs of the skull, and the appropriate side of the head should be shaved during preparation of the theatre trolleys. The patient is placed on the table on his side, with a soft pad supporting the head. If he is restless his wrists are fixed to the table by wide zinc-oxide strapping, not restrained by a nurse. Another broad band of strapping from side to side across the pelvis prevents his rolling off the table. The proposed incision—2 in. long—is marked out with a scratch or dye, infiltrated with 10 ml. of local anæsthetic (adrenaline must not be added for it increases blood-pressure and bleeding), and surrounded by drapes. Most of the anæsthetic is injected

into and beneath the scalp and little or none into the temporal muscle. Suction apparatus is a necessity and diathermy very desirable.

The incision.—Three of the assistant's fingers must exert both firm pressure and separation on each side of the scratch to make the scalp tense, and a 2-in. incision through scalp only is made between them. If the pressure is properly applied there is no bleeding. Each finger is then withdrawn in turn to release bleeding points for attention by the surgeon, who is armed with sucker in one hand and diathermy forceps in the other. Using this technique it is best for a scrubbed nurse to wield the diathermy electrode. Sometimes a retracted artery may necessitate the assistant withdrawing one hand to avert the scalp edge with toothed forceps.

The main bogy which frightens surgeons unaccustomed to such work is that of bleeding—the brisk ooze coming from nowhere visible, of the artery spurting across the room, of messing about in a field of blood with an ill restless patient, and with fears of worse to come once inside. But it is perfectly simple. Admittedly, when incised, the scalp does not reveal its deep vessels readily as does subcutaneous tissue elsewhere, and therefore more trouble must be taken. In plain words—a hasty slash made in the side of the head will get a surgeon into trouble—done methodically it is easy.

When hæmostasis in the scalp has been achieved, a self-retaining retractor is inserted and the temporalis is incised down to the bone with either a knife or cutting diathermy. Diathermy will not work if the muscle has been made œdematous with local anæsthetic. Shreds of muscle adherent to the bone are scraped off and the bleeding points are again attended to, and only when the wound is dry is the retractor rearranged to include the muscle layer.

The *perforator* is regrettably unfamiliar to most doctors not engaged in neurosurgery and yet the feel of its use is easily acquired at the expense of a few minutes practice in the postmortem room. Its blade is sharpened to cut clockwise, and the shaft of the drill must be kept at right-angles to the skull surface. The line of a fracture, if visible, is best avoided because it tends to make the perforator bind. Pressure should be firm enough to transmit a sensation of cutting into the bone. When the point has penetrated the whole thickness of the skull the sensation is coarser—that of grinding rather than cutting. This is more easily appreciated if the speed of drilling is not too slow and timid; and it is a sign to lay aside the now dangerous perforator and use the burr, which will not harm the dura mater. The Hudson burr, an effective and safe instrument, should be used boldly to enlarge the hole to useful dimensions; for provided $^1/_8$ in. is still visible superficial to the bone, the burr cannot suddenly jump right through the skull, because of its conical form. The diagnosis of extradural hæmorrhage is confirmed by the sight of black blood just visible through the tiny hole in the inner table made by the perforator (fig. 1a). Once released by completion of the burr-hole, extradural blood-clot tends to force its way out into the wound, (fig. 1b), perhaps with a trickle of fresh arterial blood also.

If the case is comparatively late, the compressed brain may have lost its immediate power of recovery; it is locally collapsed, and the intracranial pressure is no longer sufficient to force out an appreciable quantity of clot. Such a patient is in danger, and one should not hesitate to pass a large sucker through the burr-hole, manipulating it circumferentially as far as possible and aspirating all the clot presenting until the dura is exposed at the bottom of the cavity—perhaps an inch or more beneath the bone. In such cases fresh bleeding will usually be scanty, and unless a bleeding point readily presents itself for coagulation it should be ignored for the moment.

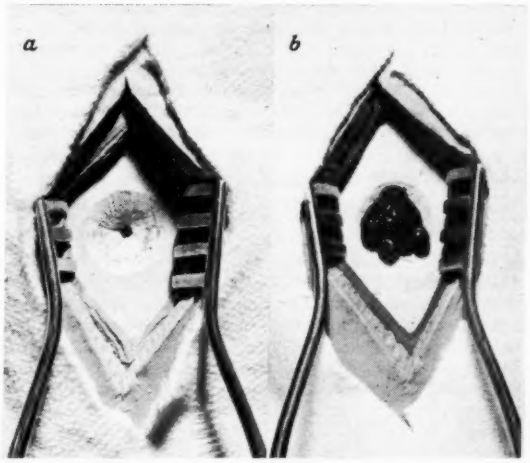


Fig. 1—(*a*) Making a burr-hole: enough has been done by the perforator, and black clot is just visible through a small hole in the inner table of the skull. (*b*) Clot extruding after enlargement of the hole to about 1 cm. with a burr proves the diagnosis of extradural hæmorrhage.

In the fulminating case, with rapid deterioration of consciousness since injury (within, say, 30 minutes to 4 hours) and early operation when intracranial pressure is at its height, the brain will be under sufficient tension to force a more copious and useful quantity of clot to the surface.

In either of the above instances the general surgeon has two courses open to him:

1. After sucking away presenting clot, he may do nothing further except to suture the scalp closely. When this is completed a dilated pupil may already have diminished in size. During the journey to a neurosurgical centre bleeding and extrusion of clot tend to make a tense swelling beneath the scalp. Blood may ooze through the wound a little, but the patient will not bleed to death. The reason for insistence on absolute hæmostasis in scalp and temporal muscle is now apparent, for bleeding from these sources would lose all the advantage gained by decom-

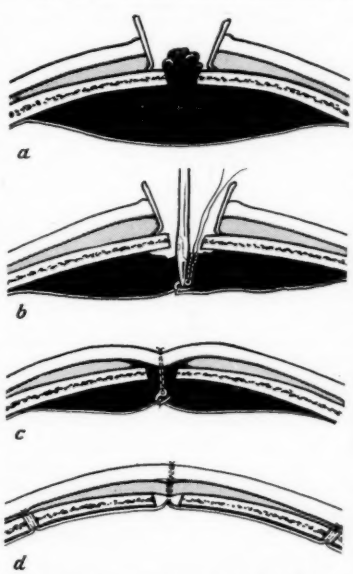


Fig. 2—Sectional diagrams depicting: (*a*) spontaneous extrusion of extradural clot after use of the burr; (*b*) the dura mater, which is lax and wrinkled, transfixed by the dura-elevating needle; (*c*) the emergency operation completed; and (*d*) the normal relations after craniotomy.

pression. For the same reason, on no account must a firm crepe bandage be applied to the head, for pressure on the scalp is pressure on the brain, and it entirely defeats the object of decompression. The surgeon should personally supervise the application of a loose cotton bandage. In my experience this method allows about 30 minutes' grace in a rapidly progressing case with fresh bleeding; and after this the pupil again dilates.

2. The safer course is to hitch up the dura to the scalp by means of a specially designed hooked needle. The dura is transfixed with the (previously threaded) needle mounted on a needle-holder, either before or after bold aspiration of all clot within reach. It is not even necessary to see the dura, a fold of which is caught up quite easily after the first or second " scrape along the bottom " (fig. 2b). As soon as good purchase is obtained, one end of the thread is passed through a large bite of scalp at the top of the wound. After a few moments of rather firm steady traction, the suture is tied. The surgeon should not be disappointed if the dura does not rise completely to the skull, for there is considerable suction beneath it, and the brain takes time to expand. The needle is shaped to avoid damage to any underlying cerebral blood-vessel. Again temporalis is left gaping, fresh bleeding is ignored, and the scalp is sutured in one layer (fig. 2c). This method should give considerably longer than 30 minutes' grace for travelling time. Though clot beneath the temporal lobe and round the periphery remains to be dealt with at the definitive stage, dural anchorage roughly at the centre of the depression relieves the brain to some extent, and especially prevents further depression due to fresh or continued bleeding.

Either of the above immediate operations should take only 20 minutes, even if it is the surgeon's first adventure in this field.

Siting of the Burr-hole

An extradural hæmorrhage from a torn middle meningeal artery (much the commonest cause) which is endangering life is of at least 3 in. diameter; hence a burr-hole anywhere within this circumference will find it (fig. 3). One need not depend on measurements to expose the middle meningeal artery itself; no useful purpose is served by exposing the artery in the temple because the bleeding is very often far down on the floor of the middle cranial fossa. Unless radiographically a fracture has been demonstrated crossing the groove of the posterior branch of the middle meningeal artery, a burr-hole should be made in the anterior position (A in fig. 3), roughly midway between eye and ear. If the search here meets with no success or with a thin film of clot only, a second hole should be made 3 in. behind and slightly above it (B in fig. 3).

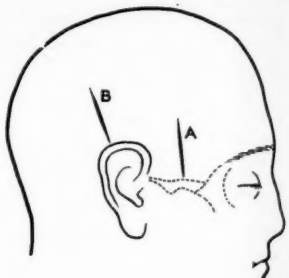


Fig. 3—In the great majority of cases of middle meningeal hæmorrhage, exposure at either A or B will find it.
The incisions need not be oblique, but this conveniently corresponds with the temporal muscle-fibres.

When hemiparesis is the only lateralising sign, negative findings at both A and B may be taken as evidence of cerebral contusion or laceration. The dura should not be incised unless it is obviously blue. (I have attributed hemiparesis to an ipsilateral extradural hæmorrhage once only; had not the weakness recovered immediately the clot was evacuated, I should have had to invoke a contralateral cerebral contusion.) If the patient is already at a neurosurgical centre fruitless explorations at the rarer sites (e.g., under the frontal lobe) may be cut short by angiography. But such explorations are necessary only when temporal swelling is absent and the scalp injury or

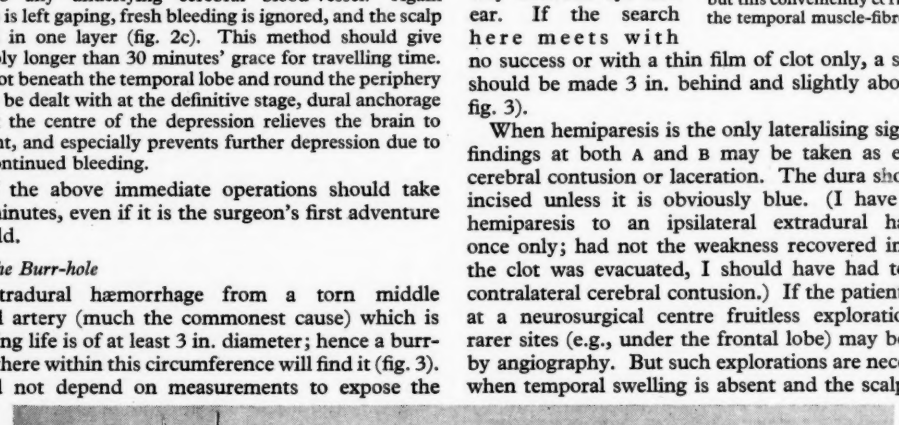


Fig. 4—The basic instruments for the emergency operation for extradural hæmorrhage.
From left to right: knife, toothed forceps, large sucker, diathermy forceps, diathermy electrode, self-retaining retractor, periosteal elevator, tube of strong braided silk, Hudson brace with no. 4 perforator bit and matching burr, needle-holder and dura-elevating needle, towel clips, scissors, and artery forceps. (The dura-elevating needle is made flat from tantalum sheet; it can be used only for this purpose, and no other needle will serve.)

fracture is remote from the temple—and these cases are best dealt with from the first by a neurosurgeon.

THE DEFINITIVE OPERATION

This neurosurgical procedure is performed through a standard osteoplastic flap only after the emergency operation has been completed.

The turning of a flap has previously been recommended for extradural hæmorrhage. Hooper (1959) said it was sometimes necessary, and Loyal Davis (1946) favoured it; but Oliver (1958) was the first to rationalise craniotomy by previously determining the extent of the clot. Craniotomy has probably not become standard neurosurgical practice for two reasons: (1) because surgeons thought at the moment it would be quicker to nibble away " to the size of a florin ", and to secure the bleeding-point with the aid of suction, diathermy, ligatures, or match-sticks, and (2) because, though the flap might be superior, turning it would be calamitous if an extradural clot were either not found or found in an unexpected position.

For the past 5 years I have used the temporal burr-hole to confirm the diagnosis, to relieve excessive pressure, and to measure—by feeling with a Gigli-saw guide—the extent to which the dura has been stripped. For the last purpose Oliver (1958) uses a malleable probe, and this is possibly better than a guide, which I have sometimes found to give a false measurement on striking a bony irregularity.

In this respect the emergency operation differs when done by a neurosurgeon. If this stage-I operation has already been performed elsewhere, the burr-hole is reopened. A seeker introduced through the clot as far as it will go is withdrawn and placed in a corresponding position over the scalp. A dye mark is made $^1/_2$ in. beyond its tip. In this way probings repeated in anterior, posterior, and upward directions determine the scalp incision. The ring of burr-holes, sited $^1/_2$ in. within the incision, then corresponds with the limits of the clot in all directions except downwards, where clot may be assumed to extend beneath the temporal lobe. The wide bone removal facilitates the search for bleeding over the floor of the middle fossa; it makes possible complete removal of all clot, and control of the many small bleeding-points which result from separation of bone from dura—and which need attention just as much as in dural separation at any craniotomy. During reposition of the bone-flap the dura in the centre of the field is hitched up to the temporalis by a stitch passing through the stage-I burr-hole, which has been left open during craniotomy.

Liaison

Neurosurgical centres welcome telephone consultations with any hospital holding a case of head injury which is deteriorating. The likelihood of extradural hæmorrhage, correlation between its possible position and the site of any visible injury to the scalp, degree of urgency, and other injuries the patient may have sustained, all must be discussed, and the plans for a given case should be put into action before even one pupil is fully dilated. In extradural hæmorrhage the degree of urgency correlates with the rate of bleeding; the more profuse the hæmorrhage the more rapid the patient's downward course and the more likely he will need immediate treatment on the spot. For instance, a patient conscious on arrival with pupils of 4 mm. who becomes restless or drowsy and whose pupil enlarges to 7 mm. within an hour, should not be moved to a neurosurgical centre 2 hours' journey away; he should have his emergency burr-hole completed within 30 minutes of the telephone consultation, and meanwhile an ambulance should be organised to stand by. As soon as the diagnosis is confirmed by burr-hole, a message is sent asking the police to escort the ambulance (the police are most obliging, enter into the spirit of the emergency, and, if the truth be told, rather enjoy it!). Unconscious cases are transported prone, for a tracheostomy and aspiration of vomit on arrival diminishes the patient's chances of survival.

Conclusions

Responsibility for the treatment of middle meningeal hæmorrhage has, with the development of fast transport and neurosurgical services, shifted too universally to remote specialised units. To reduce mortality, in selected cases, the treatment should be shared, and the more urgent the case, the more desirable are a general surgeon's services.

All hospitals accepting major accidents should carry certain instruments (fig. 4) enabling a lifesaving burr-hole to be made, and both consultant surgeons and resident surgical officers should be familiar with their use. They are best kept in a special drum, autoclaved at intervals.

I have found that the technique of saving life by emergency operation is aided by a special needle enabling the dura mater to be elevated through a burr-hole. After personal tests I think it is worthy of trial by general surgeons, for its value can only be proved on a large number of cases in which two-stage treatment is necessary.

The orthodox creeping craniectomy for extradural hæmorrhage is clumsy, inaccurate, and often slow. I would even, with some trepidation and due homage to its honourable history, condemn it as no longer worthy of inclusion among neurosurgical techniques.

Instruments mentioned in this article may be obtained from Messrs. Lewis Bros., Marylebone High Street, London, W.1.

REFERENCES

Davis, L. (1946) The Principles of Neurological Surgery; p. 99. London.
Hooper, R. (1959) *Brit. J. Surg.* **47**, 71.
McConnell, A. A. (1957) *Lancet*, i, 481.
Oliver, L. C. (1958) *Post Grad. med. J.* **14**, 524.
Symonds, C. P., Jefferson, G. (1935) *Brit. med. J.* ii, 677.

THE SMALL BLOOD-VESSELS OF THE CONJUNCTIVA AND NAILBED IN DIABETES MELLITUS

JACOB LANDAU
M.D. Vienna
CLINICAL ASSOCIATE PROFESSOR, DEPARTMENT OF OPHTHALMOLOGY

ELI DAVIS
M.Sc., M.D. Manc., M.R.C.P.
LECTURER, CHIEF, MEDICAL OUTPATIENT CLINIC C
ROTHSCHILD HADASSAH UNIVERSITY HOSPITAL,
HEBREW UNIVERSITY-HADASSAH MEDICAL SCHOOL,
JERUSALEM, ISRAEL

WITH the renewed interest in the microcirculation, Ditzel et al. (1958) have examined the small blood-vessels of the conjunctiva in diabetes mellitus and have reported significant findings. In the present work, following on the examination of the small vessels of the conjunctiva and nailbed in health and certain diseases (Davis and Landau 1960), our findings in diabetes are reported.

Methods

The group consisted of 75 diabetic patients, of whom 22 were between forty and fifty-six years old and the remainder above that age. The blood-pressure was raised in 25 and normal in 50. Of the latter, 28 showed signs of arteriosclerosis of heart, cerebral vessels, or peripheral

vessels. Diabetic retinopathy was present in 20 patients and included all grades of severity. The duration of the diabetes was less than one year in 2 patients, one or two years in 22, three to five years in 17, six to ten years in 28, and fifteen to twenty-two years in 6.

The conjunctival and nailbed vessels were examined by slit-lamp and microscope, by the techniques already reported (Landau and Davis 1957), and often photographed. The diameter of representative vessels was measured. In all patients the small blood-vessels were investigated for:

1. Venous congestion in the conjunctiva, and congestion of the venous limb of the nailbed capillary. In over 70% of healthy persons the smaller venules of the conjunctiva do not exceed 25 μ in diameter. When the diameter of these vessels exceeded 33 μ they were called congested (fig. 1). The venous limb of the nailbed capillaries in health does not exceed 12 μ in diameter. A diameter greater than 12 μ was called congested (fig. 3).

2. Severe capillary narrowing. A capillary diameter of 3·5 μ or less was termed severe narrowing. In the nailbed the measurement is of the arterial limb of the capillary.

3. The presence of an arteriosclerotic pattern (Davis and Landau 1960) in conjunctiva and nailbed (figs. 2 and 4).

4. The height of the terminal digital vessel blood-pressure (Davis 1953, Davis et al. 1959).

5. Micropools (we prefer this non-committal term to microaneurysms) of all types in the conjunctiva were sought, examined, and photographed (Cook 1954).

Exactly the same blood-vessel investigations were done on 65 healthy persons, 140 patients with hypertension, and 110 patients with clinical complications of arteriosclerosis.

Results

The results are given in the table. The following features were found in diabetes mellitus:

1. Venous congestion was very common both in the conjunctiva and in the venous limb of the nailbed capillary.

2. Severe capillary narrowing in the conjunctiva was commoner than in any group other than hypertension, and was seen particularly in diabetics with severe complications.

3. An arteriosclerotic pattern in the conjunctiva was commoner than in any group other than arteriosclerosis. The pattern was also common in the younger diabetics investigated, occurring in 8 of the 22 patients aged forty-six to fifty-six and in 4 of the 8 patients aged forty to fifty. The pattern consists essentially of straight, long, thin unkinked arterioles, accompanied by parallel or sinuous dilated venules.

4. Blood-pressure in the terminal digital vessel was found to be high in 10 of the 50 diabetics without hypertension and in 13 of the 25 diabetics with hypertension. The hypertensive diabetics with high terminal-digital-vessel pressure were prone to severe complications.

5. Micropools were not infrequent, but not commoner than in hypertension.

A characteristic blood-vessel picture emerged for diabetes mellitus in general, but not a diagnostic picture

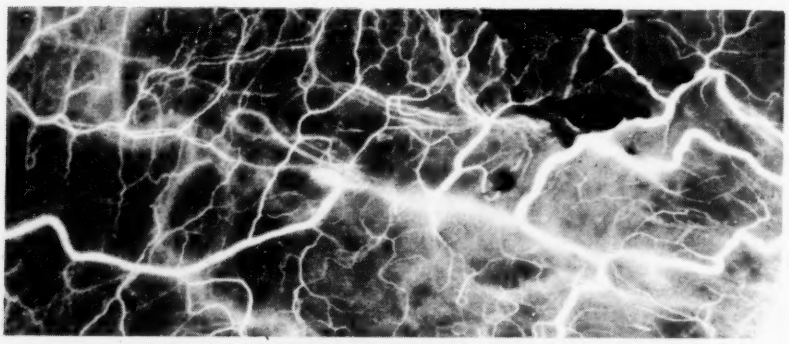


Fig. 1—Venous congestion in conjunctiva of diabetic (×11·5).

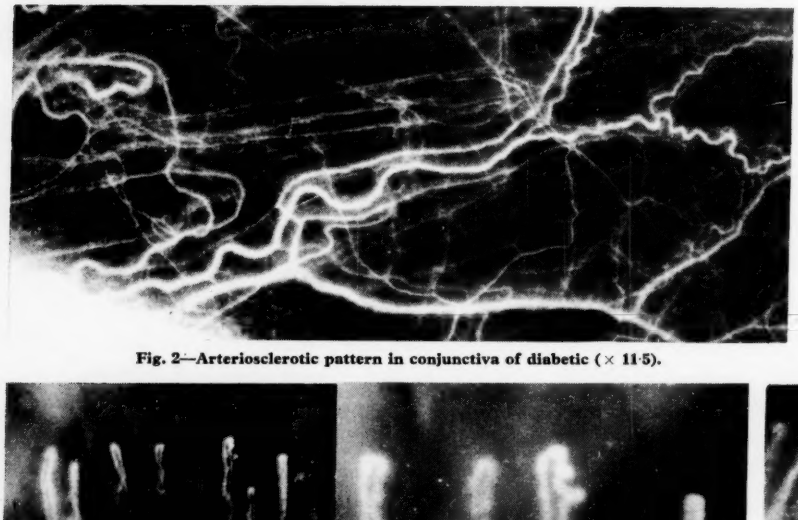
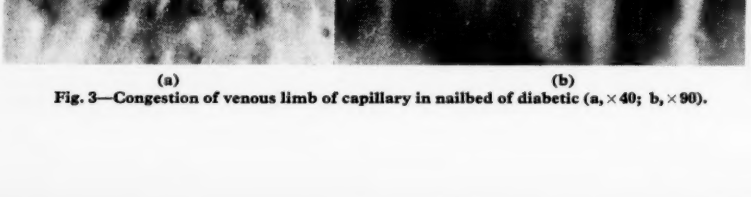


Fig. 2—Arteriosclerotic pattern in conjunctiva of diabetic (× 11·5).



(a) (b)

Fig. 3—Congestion of venous limb of capillary in nailbed of diabetic (a, ×40; b, ×90).

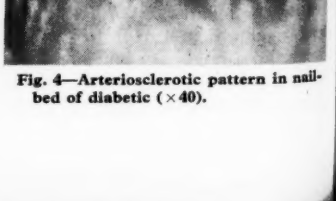


Fig. 4—Arteriosclerotic pattern in nailbed of diabetic (×40).

CAPILLARY FEATURES AT AGE 40 OR ABOVE (INCIDENCE %)

—	Healthy persons no. (65)	Hypertension (140)	Arteriosclerosis (110)	Diabetes mellitus (75)
Venous congestion:				
Conjunctiva	28	22	32	60
Nailbed, venous limb of capillary	8	14	7	49
Severe capillary narrowing:				
Conjunctiva	6	53	10	43
Nailbed	4	33	13	15
Arteriosclerotic pattern:				
Conjunctiva	10	28	71	45
Nailbed	12	24	43	24
High terminal-digital-vessel pressure	3	48	11	31
Micropools	5	24	19	25

for individual patients. When the 75 diabetic patients were divided into two groups, above and below fifty-six years old, no conspicuous differences emerged. The incidence of venous congestion was not influenced by age. In the age-group forty to fifty, the arteriosclerotic pattern was commoner in diabetics than in any other condition investigated (except arteriosclerosis with clinical complications). As regards the frequency of the various findings, only severe capillary narrowing in the conjunctiva appeared to be related to the duration of the diabetes. The 6 severest examples of diabetic retinopathy were found in diabetes of duration of four, five, eight, ten, eighteen, and twenty-two years, while the severest capillary narrowing in conjunctiva or nailbed—usually associated with increased pressure in terminal digital vessels—was seen in 13 patients with a duration of four to ten years (mean seven years), in 1 with a duration of two years, and in 4 with a duration of half or one year. Severe capillary changes, as distinct from the frequency of the various changes, were commonest in diabetes of long duration.

Discussion

As the diabetic patients were all over forty, the findings reported are those of middle age and the old. Venous congestion was the most prominent and common finding. In this we confirm Ditzel (1956) and support Ballantyne (1945) who demonstrated venous congestion in the retina in diabetes. Our finding of frequent and well-marked congestion of the venous limb of the nailbed capillary strikingly confirmed one of the basic lesions of diabetes, emphasised hitherto only in the retina and conjunctiva.

The high incidence in diabetics—particularly the younger ones—of the special pattern of the small vessels which we have shown to be characteristic of arteriosclerosis is further evidence of the close connection between diabetes and arteriosclerosis, and the tendency of the younger diabetic to arteriosclerosis. In some diabetics the pattern was the first evidence of arteriosclerosis.

The severe capillary narrowing seen in the conjunctiva in diabetes is similar to that described by us in hypertension and conformed to the conjunctival vascular pattern-change II of Ditzel (see below). The incidence of this narrowing in the 50 diabetics with normal blood-pressure was much the same as in the 75 diabetics in the whole series, including the 25 hypertensive patients. Venous stasis could result in increased terminal arteriolar and capillary blood-pressures.

As for micropools in the conjunctiva (Ashton 1949, 1959, Friedenwald 1950, Cook 1954, Ditzel 1959), they were equally common in hypertension and diabetes, somewhat less common in arteriosclerosis, and rather rare in the healthy. We have also found micropools from time to time in patients with everyday chronic medical diseases, such as chronic bronchitis and chronic arthritis, in the absence of diabetes, hypertension, or clinical arteriosclerosis. Of the diseases studied, only in hypertension did the incidence of micropools reach that of diabetes.

In diabetes Ditzel (1956) laid stress on the occurrence in the conjunctiva of venous congestion, capillary elongation, and intravascular red-cell aggregation. The present work confirms (and extends) the finding of the venous congestion; but, while we have often seen capillary elongation and red-cell aggregation, our non-diabetic patients above the age of forty have shown them quite often. It is possible that capillary elongation is more specific for the young diabetic (Ditzel and Duckers 1957).

Ditzel et al. (1958) have described two abnormal vascular conjunctival patterns in diabetes. Vascular pattern change I was characterised by a general vascular distension. The ratio of the arterial/venous diameter, normally 1/3 to 1/2, became 1/4 to 1/8. Change II was marked by a general constriction of all vascular elements. Most true capillaries were completely invisible and the tissue ischæmic. Many arterioles were closed. All his diabetics with conjunctival vascular pattern-change II had severe vascular disease (retinopathy and nephropathy), while those with change I had less evidence of vascular disease, but more than in those diabetics with normal conjunctivæ. Our 75 patients included 11 with severe diabetic and vascular complications. Of these 11, 8 had pattern-change II and 3 change I. We agree that pattern II is common in severe diabetes, but we have shown it to be a feature of severe hypertension (Landau and Davis 1957, fig. 3; Davis and Landau 1958) and have also seen the pattern in other conditions.

Diabetes was associated with characteristic but not pathognomonic changes in the small vessels of conjunctiva and nailbed—namely, venous congestion and congestion of the venous end of the capillaries, an arteriosclerotic pattern in the conjunctiva (particularly in the age-group forty to fifty), severe capillary narrowing in the conjunctiva, and an increased incidence of high pressure in the terminal digital vessels.

Summary

The small blood-vessels of the conjunctiva and nailbed were examined in 75 diabetics and compared with those of 140 hypertensive and 110 arteriosclerotic patients, and 65 healthy persons—all aged forty or more.

Venous congestion in the conjunctiva was found in 60% of the diabetics. The venous limb of the nailbed capillary was also commonly congested. The basic diabetic lesion of capillary congestion on the venous side has thus been found elsewhere than the eye.

An arteriosclerotic pattern of the small vessels of the conjunctiva was common in diabetics, and particularly frequent in comparison with the other conditions at ages from forty to fifty.

Severe capillary narrowing in the conjunctiva was common, and a high pressure in the terminal digital vessels not uncommon, in diabetics.

The incidence of conjunctival micropools in diabetes was appreciable (25%); but although much commoner than in the healthy they were only slightly commoner than in arteriosclerosis and no commoner than in hypertension.

Diabetes was associated with characteristic but not pathognomonic changes in the small blood-vessels of the conjunctiva and nailbed.

Thanks are due to Mr. M. Ivry for photographs and skilled observations.

REFERENCES

Ashton, N. (1949) *Brit. J. Ophthal.* **33,** 407.
— (1959) *Lancet*, ii, 625.
Ballantyne, A. J. (1945) *Arch. Ophthal.* **33,** 97.
Cook, C. A. G. (1954) *17th Int. ophthal. Congr.* **3,** 1878.
Davis, E. (1953) *Arch. intern. Med.* **91,** 715.
— Landau, J. (1958) *Acta med. or., Jerusalem*, **17,** 11.
— — (1960) *Angiology*, **11,** 173.
— — Keleti, L. (1959) *Amer. Heart J.* **57,** 747.
Ditzel, J. (1956) *Circulation*, **14,** 386.
— (1959) *Lancet*, ii, 849.
— Duckers, J. (1957) *Acta pædiat., Uppsala*, **46,** 535.
— Sargeant, L., Hadley, W. B. (1958) *Arch. intern. Med.* **101,** 912.
Friedenwald, J. S. (1950) *Amer. J. Ophthal.* **33,** 1187.
Landau, J., Davis, E. (1957) *Lancet*, i, 1327.

PSEUDOMONAS PYOCYANEA WOUND INFECTION
AN OUTBREAK IN AN ORTHOPÆDIC UNIT

M. SUSSMAN
B.Sc., Ph.D. Leeds, M.I.Biol.
ASSISTANT BACTERIOLOGIST *

J. STEVENS
M.A., M.B. Cantab., F.R.C.S.
LECTURER IN ORTHOPÆDICS

From the Departments of Bacteriology and Orthopædics, The University, Glasgow

IN well-run orthopædic units wound infection is unusual and outbreaks due to *Pseudomonas pyocyanea* must be rare. In burns units and urological units this organism is a well-known hazard.

The outbreak, described here, among patients under treatment for fractures, was unexpected and disquieting.

Outbreak and Investigation

On April 28, 1959, a patient (case 1, table I) was admitted to the male ward of the unit. He was unconscious and had severe injuries of the head, chest, and lower limbs. Treatment with 1,000,000 units of penicillin four-hourly was started, and next day an emergency tracheostomy was carried out in the " plaster room ". In spite of regular bronchoscopy, a tracheobronchitis developed and *Ps. pyocyanea*, *Staphylococcus aureus*, and β-hæmolytic streptococci were cultured from a swab of the bronchial secretions taken on April 30. The strain of *Ps. pyocyanea* was sensitive to streptomycin and chloramphenicol.

Six days later 3 other patients (cases 2–4) were found to have *Ps. pyocyanea* wound infections and it seemed likely that case 1 was disseminating the organisms as an aerosol from the tracheostomy tube. Cases 1, 2, and 4 were accordingly transferred to a side-ward for barrier nursing.

Case 3, however, was a patient in the female ward.

In the male ward, examination of dust, curtains, and blankets, as well as air sampling with the Bourdillon slit-sampler in the neighbourhood of case 1, revealed a low level of air contamination (100 colonies per c. ft.) and no *Ps. pyocyanea*. These negative findings, and the infection of a patient in the female ward, attracted attention to the plaster-room, where case 1 had had his tracheostomy and where all 4 patients had received treatment. It was now discovered that the plaster-encrusted bucket (fig. 1) used for soaking plaster-of-paris bandages contained *Ps. pyocyanea* among other organisms. As *Ps. pyocyanea* was not found elsewhere in the plaster-room (table II), the bucket was thought to be the source, and it was replaced.

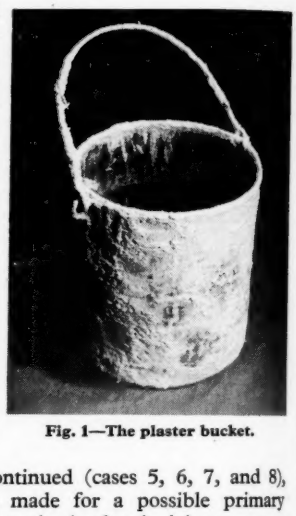


Fig. 1—The plaster bucket.

Infection, however, continued (cases 5, 6, 7, and 8), and further search was made for a possible primary source, assuming now that the bucket had been secondarily contaminated.

Cultures of plaster-of-paris in the form of powder and ready-made bandages grew no *Ps. pyocyanea*, but this organism was found in large numbers in cultures from the cellulose wadding (" wood wool ") used as padding under all plaster casts applied for fresh fractures. All the infections were in patients to whom padded plasters had been applied for the treatment of fractures which were either compound or were accompanied by skin abrasions in the region included in the plaster. In all the compound

* Present address: Medical Research Council Unit for Experimental Virus Research, The University, Glasgow, W.1.

TABLE I—CASES IN ORDER OF THEIR DISCOVERY

Patient	Fractures	Operation	Initial treatment	Pyocyanea isolated	Result
1	Tibiæ and fibulæ (one compound)	April 25 (tracheostomy)	Debridement. Long leg plaster	April 30	Died from head injury
2	Compound Pott's	April 23	Debridement, internal fixation. Short leg plaster	May 6	Healed, second intention
3	Compound tibiæ and fibulæ	April 2	Debridement, open reduction. Steinmann pins in long leg plaster	May 6	Pin-track infection only. Healed
4	Bilateral os calcis (one compound). Tibia, closed	April 22	Debridement, manipulation. Long leg plaster	May 6	Split skin graft to heel
5	Compound tibia and fibula	May 3	Debridement, closed reduction. Long leg plaster	May 14	Healed, second intention
6	Right tibia and left Pott's. Abrasion	May 7	Manipulation and long leg plaster. Open reduction and short leg plaster	June 22	Split skin graft, right shin
7	Compound tibia and fibula with degloved skin	May 30	Internal fixation. Skin defatted and put back	June 15	Infection at fracture site. Late pedicle graft
8	Pott's. Abrasions	June 27	Manipulation and plaster. *	July 22	Split skin graft, ankle

* Initially treated as outpatient in casualty department.

TABLE II—ORGANISMS ISOLATED IN PLASTER-ROOM

Source	Organisms	Degree of contamination
Air	*Bacillus spp., Staph. albus, Sarcina spp.*, coliforms, moulds.	40 colonies per c. ft.
Dust.. ..	*Bacillus spp., Cl. welchii*	Moderate
Non-sterile instruments*	No growth	..
Table top ..	No growth	..
Floor ..	*Bacillus spp., Cl. welchii*, coliforms	Severe
Rubber mats	Coliforms, *Staph. albus, Staph. aureus*	Severe
Water-supply	*Bacillus spp.* †	Slight (c. 40 colonies per ml.)
Air-filters	No growth ‡	..

* e.g., plaster shears.
† Probably derived from the tap.
‡ The filters were impregnated with soot. Tests showed this to be toxic for a laboratory strain of *Staph. albus*.

fractures skin closure had been achieved after wound excision, and the suture line had been covered with several layers of sterile gauze and a layer of sterile cotton-wool before cellulose wadding and plaster-of-paris were applied. Some, but not all, operations had been done after the application of a pneumatic tourniquet, the limb having been exsanguinated by an Esmarch bandage. The abrasions accompanying simple fractures had been cleaned with cetrimide and chlorhexidine before being covered with sterile gauze, cellulose wadding, and plaster.

The Esmarch bandage kept in the plaster-room was found to be heavily contaminated with *Clostridium welchii*, *Staph. aureus*, *Staph. albus*, coliforms, and aerobic spore-forming bacilli, but *Ps. pyocyanea* was not isolated.

Fig. 2—Extent of ecthyma gangrenosum in patient 8.

Effect of Infection

The effect of *Ps. pyocyanea* infection is best illustrated by examples.

PATIENT 6 had simple fractures of the left ankle and right upper tibia. The left Pott's fracture was treated by operative screw fixation of the medial malleolus and did not become infected. The right tibial fracture was associated with multiple abrasions on the shin and did not have the covering of sterile wool that was used for the left ankle. Because of associated instability of the knee, the long leg plaster on the right leg was untouched for six weeks. On its removal a moderate amount of green pus was encountered and an area of full-thickness skin loss, 3×6 in., was found in the region of the skin abrasions. Culture of the pus produced a pure growth of *Ps. pyocyanea*. The raw area cleaned up rapidly with daily dressings of 'Polybactrin' (polymyxin-bacitracin-neomycin) spray and soft-paraffin gauze, and was ready for successful split-skin grafting after two weeks.

PATIENT 7 had sustained a severe compound fracture of the right tibia and fibula with an extensive "degloving" injury of the overlying skin. Screws were used to fix the fracture and total cover was obtained using the skin available, though part of this was "defatted" and used as a full-thickness free graft. Sterile gauze and wool were covered with cellulose wadding before plaster-of-paris was applied. An area 2×3 in. of the "graft" sloughed, and the associated *Ps. pyocyanea* infection called for removal of the bone screws. Subsequent treatment included sequestrectomy and required the transfer of a tubed skin pedicle from the abdomen. This was timed to give full-thickness skin cover of the incompletely healed fracture site by the time the infection had been controlled.

In the most troublesome cases, the infection led to full-thickness skin loss. The appearances (fig. 2), which have been described (Wilson and Miles 1955) as "ecthyma gangrenosum", were uniform in that the area of skin loss became well demarcated and the dead black slough separated relatively early to leave a base that was rapidly made clean enough for grafting. In spite of this ease of handling of the complication, treatment was lengthened in nearly all the patients.

Non-pathogens

Non-pathogenic aerobic spore-forming bacilli were isolated from the cellulose wadding and from apparently infected wounds of the patients listed in table III, none of whom had *Ps. pyocyanea* infections. These patients showed no ill effects and they are reported only as further evidence that the *Ps. pyocyanea* infections originated in the cellulose wadding.

Sterilisation of Cellulose Wadding

As soon as it was shown that the cellulose wadding was contaminated with *Ps. pyocyanea*, sterilisation was undertaken.

Rolls of wadding 3 in. and 6 in. wide are supplied to the hospital in packages of 12. The rolls are $2^1/_4$ in. and $2^3/_4$ in. in diameter; they are relatively tightly wound and have a covering of tissue paper which is open at both ends.

Tests with Browne's steriliser control tubes indicated that a sterilising temperature was attained in the centre of rolls. Additional tests with thermocouples in an experimental autoclave showed that the time-lag between the temperature in the inside of the dressings drum and the temperature in the centre of a roll was insignificant. Autoclaved wadding proved to be sterile.

All the wadding has since been autoclaved at 15 lb. (121°C) for twenty minutes before use and no further incidents of infection have come to light. The material deteriorates a little through sterilisation but not enough to interfere with its use.

TABLE III—CASES WITH AEROBIC SPORE-FORMING BACILLI *

Patient	Admission	Fracture	Operation	Treatment	Positive swab
9	June 2	Closed tibia and fibula; blisters	June 2	Manipulation and plaster †	June 2
10	June 2	Compound tibia and fibula	June 2	Debridement, open reduction and suture	June 24
11	Aug. 16	Closed tibial table	Aug. 16	Open reduction internal fixation and plaster	Aug. 20

* The aerobic spore-forming bacilli isolated were unlike those isolated from the water-supply but similar to those isolated from the wadding.
† Initial treatment on May 30 given elsewhere. Admitted with plaster blisters.

Discussion

In these cases *Ps. pyocyanea* almost certainly reached the wounds, or their sterile dressings, in water which had been expressed from a wet plaster bandage and contaminated by passage through the infected cellulose wadding. Oozing or bleeding can help to form a "nutrient bridge" by which organisms may migrate. If plaster bandages are soaked in contaminated reservoirs (e.g., the bucket), the hazard is even greater.

Though the Esmarch bandage was a potential source, no actual infections from its use were discovered. This may have been because the skin was carefully cleaned before any operative procedure and wounds associated with compound fractures were always excised. Nevertheless, it seems desirable to treat Esmarch bandages regularly with an effective antiseptic.

The most important lesson of this outbreak is the importance of proper sterilisation of all dressings—even those remote from actual wounds.

Summary

An outbreak of *Pseudomonas pyocyanea* infection in an orthopædic unit was traced to contaminated cellulose wadding (wood wool). The importance of routine sterilisation of all dressings—even those remote from wounds—is emphasised.

We wish to thank Prof. J. W. Howie and Prof. R. Barnes for their interest and help in this investigation.

REFERENCES

Wilson, G. S., Miles, A. A. (1955) Topley and Wilson's Principles of Bacteriology and Immunity; vol. I, p. 597. London.

CHROMOSOME COUNT IN A HERMAPHRODITE WITH SOME FEATURES OF KLINEFELTER'S SYNDROME

R. R. GORDON
M.C., M.D. Glasg., M.R.C.P.
CONSULTANT PÆDIATRICIAN, CITY GENERAL HOSPITAL, SHEFFIELD

F. J. P. O'GORMAN
M.B. Glasg., F.R.C.S.E., M.R.C.O.G.
CONSULTANT SURGEON AND UROLOGIST, CITY GENERAL HOSPITAL

C. J. DEWHURST
M.B. Manc., F.R.C.S.E., M.R.C.O.G.
SENIOR LECTURER IN OBSTETRICS AND GYNÆCOLOGY, UNIVERSITY OF SHEFFIELD; HONORARY CONSULTANT OBSTETRICIAN AND GYNÆCOLOGIST, CITY GENERAL HOSPITAL

C. E. BLANK
M.B. Wales, Ph.D. Lond.
LECTURER IN MEDICAL GENETICS, UNIVERSITY OF SHEFFIELD

From the City General Hospital, Sheffield, and the Department of Genetics, University of Sheffield

IN 1956 Tijo and Levan, analysing the chromosome complement of normal lung fibroblasts derived from a series of aborted human fœtuses, demonstrated that these cells each had 46 chromosomes. Shortly afterwards Ford and Hamerton (1956), working with testicular tissue, confirmed this figure. It is now accepted that man has a diploid chromosome number of 46–22 pairs of autosomes and a single pair of sex chromosomes, XX in the female and XY in the male. The revolutionary techniques used by these workers were soon applied to the study of human congenital malformations, and at least twenty different chromosomal anomalies have been shown to be associated with clinical abnormalities. Undoubtedly other similar associations remain to be discovered.

Among the first human disorders to be analysed for chromosome number and morphology was Klinefelter's syndrome (Jacobs and Strong 1959, Ford et al. 1959a and b, Stewart 1959, Crooke and Hayward 1960, Bergman et al. 1960). The chromatin-positive cases of Klinefelter's syndrome so far described have 47 chromosomes—presumably 22 pairs of homologous autosomes and an XXY sex-chromosome-complement.

We report here a case which presented some of the clinical features of Klinefelter's syndrome—a diagnosis which was strengthened by the finding of chromatin-positive nuclei in the buccal smear. Chromosome analysis, however, did not confirm this diagnosis and stimulated a search for ovarian tissue. The patient, is, in fact, a lateral hermaphrodite with an ovary and a testis.

Cases of hermaphroditism are exceedingly rarely reported, and until 1959 only about 88 had been recorded (Lewis 1959). Of these, 8 have had their "chromatin-state" recorded. Only in 2 cases have the chromosome number and morphology been reported (Harnden and Armstrong 1959, Hungerford et al. 1959). We report a 3rd case.

Case-record

In 1956, at the age of 11 years, the patient presented because of pronounced penile hypospadias, the opening of the urethra being some 4·5 cm. from the tip of the glans. At that time there were no secondary sex characteristics; the left testis could not be palpated, and the right testis was in the scrotum and felt normal. In other respects he seemed a normal boy. The hypospadias was repaired by the Denis Browne operation, and the functional result was sufficiently satisfactory to justify discharge from the follow-up clinic a year later.

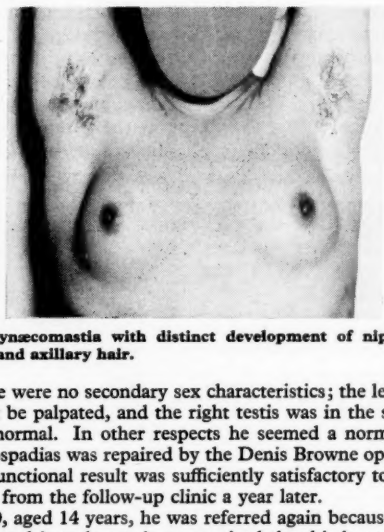


Fig. 1—Gynæcomastia with distinct development of nipple and areola, and axillary hair.

In 1960, aged 14 years, he was referred again because, as he had advanced in puberty, it was noticed that his breasts were enlarging much more than was thought to be normal for a boy of his build (fig. 1). He was finding this a very great embarrassment at school and was anxious to have something done about it. He was quite tall (5 ft. $4^1/_2$ in.) and thin (body-weight 7 st. 10 lb.) and of eunuchoid proportions (span 5 ft. 7 in.; U/L 0·87; head to pubis 30 in., pubis to feet $34^1/_2$ in. (fig. 2). His intelligence appeared to be of low average, and he was of a quiet but pleasant disposition. His voice was partially broken, but he had no facial hair. He did, however, have plenty of pubic and axillary hair, but the former was of feminine distribution (fig. 2). The right testis was in the scrotum and was of normal consistency, but felt slightly smaller than would be expected for his degree of maturity (fig. 3). The left testis could not be palpated in the scrotum, nor in the inguinal canal. He had pronounced gynæcomastia with well-developed nipples each surrounded by a distinct areola. On clinical examination the other systems were entirely normal.

Initial investigations revealed that he had a normal output of 17-ketosteroids and ketogenic steroids (3·9 and 7·4 mg. per day respectively). His white-blood-cell count was 8300 per c. mm. with a normal differential count. Female "drumsticks" were

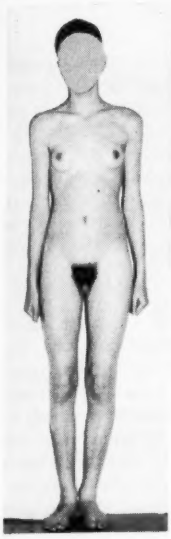


Fig. 2—Configuration of the patient, showing feminine distribution of pubic hair.

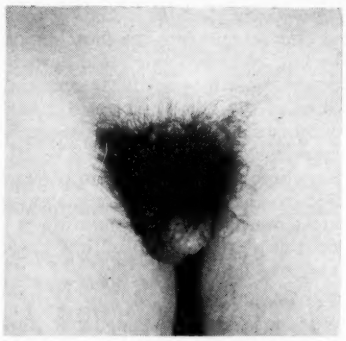


Fig. 3—Pubic hair and genitalia: the penis is of reasonable size but only right testis can be seen in scrotum.

present in the neutrophils, and the buccal smear confirmed that he was " chromatin-positive ". It was at this stage that we felt he represented chromatin-positive Klinefelter's syndrome, and accordingly it was decided that bilateral mastectomy should be undertaken. This was done, and at the same time testicular biopsy and marrow puncture were performed.

Testicular biopsy (fig. 4) showed that varying degrees of tubular atrophy had occurred as a result of intratubular fibrosis and collagen deposition: some tubules had atrophied completely. Surviving tubules were lined solely by Sertoli cells, and no evidence of spermatogenesis was present. The interstitial cells, which were somewhat reduced in quantity, were in small clumps lying in a loose stroma. The appearances were similar to those described by Ferguson-Smith (1959) and Plunkett and Barr (1956) in some cases of chromatin-positive Klinefelter's syndrome.

Chromosome analysis.—Bone marrow specimens, obtained by sternal puncture, were treated by a modification of the method described by Ford et al. (1958). Squash preparations were made from the final, Feulgen- and aceto-orcein- stained, cell suspension. These were searched systematically for cells in metaphase of mitosis. Forty-two cells, in which the chromosomes could be counted accurately, were recorded. Thirty-nine cells each contained 46 chromosomes; and in no cell were 47 chromosomes counted. The results were as follows:

No. of chromosomes				
<45	45	46	47	>47
2	1	39	0	0

Sex chromosomes XX. No chromosomal abnormality apparent.

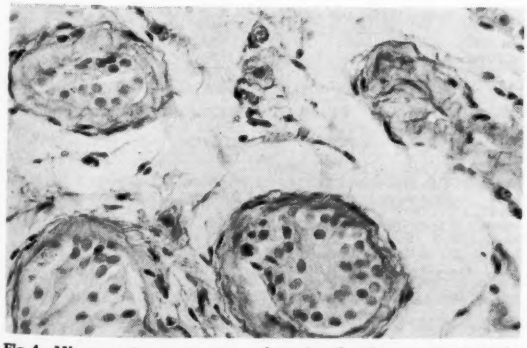


Fig. 4—Microscopic appearance of testis, showing severe atrophy and fibrosis of tubules and complete absence of spermatogenesis.

Chromosome morphology was examined in six cells. Each cell appeared to contain a set of 23 pairs of chromosomes as in a normal female.

Hormone assays showed that the excretion of urinary gonadotrophins was 24 mouse units per day (normal 8–48 mouse units). There was a normal output of 17-ketosteroids (as has already been mentioned), but the urinary excretion of œstrogens (60 I.U. per day) was in excess for a boy of this age (normal 8–26 I.U. per day).

Diagnosis.—The normal output of gonadotrophins, the high output of œstrogens, and the absence of the left testis were somewhat against the diagnosis of Klinefelter's syndrome. Above all, however, the chromosome analysis, although confirming the presence of two X chromosomes, excluded the diagnosis since the Y chromosome was absent. The most likely alternative diagnosis was hermaphroditism, with the probability that the left gonad was intra-abdominal and contained ovarian tissue.

Laparotomy.—It was, therefore, with some degree of confidence that laparotomy was carried out. On the right side of the pelvis there was no gonad and no internal genitalia. On the left side there was a normal-sized ovary and fallopian tube and a unicornuate uterus. The uterine body seemed to represent normal development of the left mullerian system, but, where the junction of the " body " and the cervix should have been, the uterus tapered away into a thickened cord which continued downwards to disappear beneath the bladder base. The uterus, tube, ovary, and as much of the thickened cord as could easily be dealt with, were removed.

Histological examination of these structures showed that the uterus had a normal muscle wall and was lined by a small amount of regenerative-type endometrium; the thickened cord had a fibromuscular wall and was lined by tall columnar mucus-secreting epithileum resembling normal endocervical tissue. The architecture of the fallopian tube was normal. The ovary contained one follicular cyst 2·5 cm. in diameter and a second smaller one; microscopically, numerous primary follicles were seen and there was one corpus albicans.

Postoperatively the boy did well, and over the next few weeks there was an increase in the urinary output of gonadotrophins to 36 mouse units per day and a decrease in the output of œstrogens (to 20 I.U. daily). These findings presumably were related to the removal of the ovary, the rise in gonadotrophins being secondary to the fall in œstrogens.

The patient was put on methyl testosterone 20 mg. daily, and it is proposed continuing with this for some time. Before his discharge from hospital, the father was told exactly what had been found and what had been done. It was our opinion, and the father agreed, that the boy was completely oriented as a male, and he certainly fitted in well with the other members of the male adolescent ward on which he was nursed during his hospital stay. The boy himself took all the surgical procedures with great calmness, and his main emotional reaction to it all was of delight at having got rid " of these things " from his chest wall.

Blood-groups.—Unfortunately, we could not make any attempt to establish mosaicism in this child, but the blood-groups were all established in detail and were as follows:

A_1, MNS, P_1+ve, CDe/CDe, Lu(a−), K(a−), Le(a+b−), Fy(a+), Jk(a−), Wr(a−), C^W−ve. Non-secretor.

Family history.—There was nothing of any great interest in the family history. He was the eldest child of healthy parents who said no such thing had ever occurred before on either side of the family. Next to him in birth order were twin boys aged 12 years, a boy aged 9 years, a girl aged 5 years, and a 2-year-old girl. All the other children were said to be normal.

Discussion

Clinical Features

When this boy first presented, the sound advice of Lewis (1959) had not been published. This advice is that hermaphroditism should always be suspected in a boy with hypospadias and an undescended testis. In the light

of the present case this seems to be sound advice. Whenever such a combination is encountered the sex chromatin should be determined.

When our patient presented for the second time, it seemed probable, on clinical grounds, that he had Klinefelter's syndrome. The hypospadias and the undescended testis, although not characteristically associated with this syndrome, could presumably occur with it. Once the buccal smear showed that the patient was chromatin-positive, it seemed almost certain that the diagnosis was correct, although the results of the testicular biopsy were not available at that stage. We had, however, established that the patient was a eunuchoid male with female distribution of pubic hair, absence of facial hair, primary microorchidism (Ferguson-Smith 1959), and considerable gynæcomastia: on these features the preliminary diagnosis was made.

Gonadal and Hormone Changes

Testicular biopsy certainly showed very considerable atrophy of the testis (Nelson 1956). Surviving tubules were lined solely by Sertoli cells and showed no spermatogenesis; other tubules showed varying degrees of intratubular fibrosis and collagen deposition. The Leydig cells were reduced in quantity—a finding previously described in some cases of chromatin-positive Klinefelter's syndrome, although an increase in their number is more common.

This absence of hypertrophy in the interstitial cells in the testis was compatible with the normal level of gonadotrophins in the urine since it is thought (Klinefelter et al. 1942) that the hypertrophy is secondary to overstimulation of the Leydig cells by pituitary gonadotrophins as a response to the underproduction of the interal secretion of the Sertoli cells. As was expected, the 17-ketosteroid excretion in the urine was perfectly normal for the patient's age, but the excretion of œstrogens was excessive for either a normal male or a patient with chromatin-positive Klinefelter's syndrome.

The ovary on the other hand was well developed and of normal size. Microscopically it showed primitive follicles and a corpus albicans, which indicated that ovulation had occurred. It was structurally a much more active gonad than the testis.

Operative Intervention

The initial operations on the hypospadias have been exceedingly successful and will enable the patient to lead a much more normal male life in the future, as will, of course, the complete bilateral mastectomy which he underwent. At the time of the mastectomy, the testicular biopsy and marrow puncture were performed so as to reduce the number of separate anæsthetics administered. We were glad that it had been done that way, when eventually, as a result of the further studies, it became clear that laparotomy would have to be undertaken. The condition found inside the pelvis was really quite striking, since on the right side there were no genitalia but on the left the ovary, tube, and left horn of the uterus were all present and of reasonable size. The findings in this case bear out the suggestion of Jost (1953) that the development of the internal genitalia on each side may depend on the nature of the gonad on that side.

The reasoning which lay behind the removal of all the female genitalia is more fully discussed later under treatment. We all agreed that if female internal genitalia and an ovary were found, as we expected, then they should be removed in their entirety.

Chromosome Analysis

This was perhaps the most important single finding in leading us away from the diagnosis of Klinefelter's syndrome, since it seems fairly certain that at least in all true cases of the chromatin-positive variety there will be an extra sex chromosome (either an X or a Y) so that the individual is genetically XXY. Hitherto chromosomes have been counted mainly in known congenital malformations to find out if there is any abnormality of number or of gross morphology. In the present case, however, it was used as a straight clinical investigation with most useful and revealing results.

Treatment

It could be safely argued that this child was more female than male in that his sex-chromosome pattern was XX, his ovary was a much more adequately functioning organ than his testis, he had some uterine tissue, and he had pronounced breast development. On the other hand, he was physically a male in general appearance and his external genitalia were masculine. He had not even a vestigial vagina. Most important of all, he was psychologically oriented as a male, and it has been strongly recommended (Marshall 1954, Hampson 1955, Money et al. 1955, Wilkins 1957) that in these cases of intersex where the individual is not completely of either sex the patients should be brought up in the sex to which they have been accustomed and to which, superficially, they appear to belong. In order to achieve this, it is necessary to remove the evidence of the other sex, so as to avoid embarrassment later on and, as far as possible, to leave the evidence of the obvious sex intact. Since the whole future of the child is at stake, it is exceedingly important to make a firm decision at the time the child is under investigation and treatment (Lewis 1959), to carry out the treatment radically at the time and then to send the patient out into the world with the greatest possible security and confidence. As with so many other things, it is doubts that may lead to trouble, and in the patient's mind these should be reduced as far as possible.

Our thanks are due to Dr. C. C. Bowley and Dr. F. I. N. Dunsford, of the Sheffield Regional Blood Transfusion Centre, for the detailed report of the patient's blood-groups; to Dr. S. Varadi, consultant hæmatologist, City General Hospital, Sheffield, for performing the marrow biopsy for the chromosome analysis; and to Dr. C. G. Paine, consultant pathologist, Jessop Hospital for Women, Sheffield, for help with the histology and for supplying the photomicrograph.

REFERENCES

Bergman, S., Reitalu, J., Nowakowski, H., Lenz, W. (1960) *Ann. hum. Genet.* **24**, 81.
Crooke, A. C., Hayward, M. D. (1960) *Lancet*, i, 1198.
Ferguson-Smith, M. A. (1959) *ibid.* p. 219.
Ford, C. E., Hammerton, J. L. (1956) *Nature, Lond.* **178**, 1020.
— Jacobs, P. A., Lajtha, L. G. (1958) *ibid.* **181**, 1565.
— Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. (1959a) *Lancet*, i, 709.
— Polani, P., Briggs, J. H., Bishop, P. M. F. (1959b) *Nature, Lond.* **183**, 302.
Hampson, J. G. (1955) *Bull. Johns Hopk. Hosp.* **96**, 265.
Harnden, D. G., Armstrong, C. N. (1959) *Brit. med. J.* ii, 1287.
Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. (1959) *Amer. J. hum. Genet.* **11**, 215.
Jacobs, P. A., Strong, J. A. (1959) *Nature, Lond.* **183**, 302.
Jost, A. (1953) *Rec. Progr. Horm. Res.* **8**, 379.
Klinefelter, H. F., Reifenstein, E. C., Allbright, F. (1942) *J. clin. Endocrin.* **2**, 615.
Lewis, E. L. (1959) *J. Urol.* **81**, 309.
Marshall, V. F. (1954) *ibid.* **72**, 77.
Money, J., Hampson, J. G., Hampson, J. L. (1955) *Bull. Johns Hopk. Hosp.* **97**, 301.
Nelson, W. O. (1956) *Acta endocr. Copenhagen.* **23**, 227.
Plunkett, E. R., Barr, M. L. (1956) *Lancet*, ii, 853.
Stewart, J. S. S. (1959) *ibid.* i, 1176.
Tijo, J. H., Levan, A. (1956) *Hereditas*, **43**, 1.
Wilkins, L. (1957) The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence; p. 285. Oxford.

Addendum

Since this article was submitted Ferguson-Smith et al. (Ferguson-Smith, M. A., Johnston, A. W., Weinberg, A. N.

Lancet, 1960, ii, 126) have reported 2 cases of hermaphroditism and de Assis et al. (de Assis, L. M., Epps, D., Bottura, C., Ferrari, I. *Lancet*, 1960, ii, 129) have reported 1 case: in all 3 cases the normal basic diploid number of 46 chromosomes was thought to be present with an XX constitution. Hirschhorn et al. (Hirschhorn, K., Decker, W. H., Cooper, H. L. *Lancet*, 1960, ii, 319), however, have described the case of an infant who is a hermaphrodite and who appears to be an XO/XY mosaic.

EXPERIMENTAL THYROIDITIS

AN APPRAISAL OF AUTOIMMUNE MECHANISMS IN ITS PRODUCTION

W. E. SHEPHERD * M.D. Manitoba
E. LIPINSKI † M.D. Brit. Columbia
H. E. TAYLOR M.D. Dalhousie, F.R.C.P.(C.), F.R.C.P.E.
From the Department of Pathology, Faculty of Medicine, University of British Columbia, Vancouver 8, B.C., Canada

Fromm et al. (1953) noted that in patients with Hashimoto's thyroiditis the serum level of gammaglobulin was raised. Others have reported positive results in colloidal-gold, thymol-turbidity, and cephalin-flocculation tests. Roitt et al. (1956) reasoned that the presence of lymphoid tissue and plasma cells in the thyroid lesion, together with these altered biochemical findings, suggested a disease of immunological significance. They reported that sera from 7 of 9 patients with Hashimoto's disease gave a positive precipitin reaction when mixed with an extract from human thyroids. In a later series (Doniach and Roitt 1957) 109 of 144 patients demonstrated this phenomenon.

About the same time, Rose and Witebsky (1956) reported the production in rabbits of antibody to injected homologous and autologous rabbit-thyroid extract mixed with Freund's adjuvant, and a histological alteration in their thyroids which resembled human Hashimoto's thyroiditis. In a later series (Witebsky et al. 1957), 32 of 35 rabbits showed thyroid lesions which to some degree paralleled the antibody titre. Recently Terplan et al. (1960) summarised the findings in experimental thyroiditis in rabbits, guineapigs, and dogs. While they noted a qualitative correlation between the demonstration of circulating antibodies and the production of thyroiditis in rabbits, no such correlation was found in either guineapigs or dogs, and even in rabbits there was no quantitative correlation between the titre of the antibodies and the severity of the thyroiditis.

On the basis of these various reports a hypothesis for the pathogenesis of Hashimoto's thyroiditis was suggested (*Lancet* 1957). Some unknown mechanism, possibly related to the disruption of the follicular basement membrane which has been described in thyroiditis (Sommers and Meissner 1954, Stuart and Allan 1958), permits the localised release of thyroglobulin from the thyroid follicles. The presence of colloid material in the interfollicular connective tissue has been demonstrated by the fluorescent-antibody technique (White 1957). In response to this extravasation, an inflammatory reaction quickly develops, with the plasma cells producing antibody to thyroglobulin. The resultant antigen-antibody reaction causes more follicular damage and increased leakage of colloid. Excess colloid eventually enters the circulation, producing a generalised antibody response. On this hypothesis Hashimoto's thyroiditis would be classified as a self-perpetuating autoimmune disease—one end-result being destruction of the thyroid with associated myxœdema.

We have re-examined some aspects of this hypothesis. First, some of the work of Witebsky et al. has been repeated in an effort to reproduce "immunological" thyroiditis, and in these experiments the antibody titres of the animals have been followed serially. Secondly, an attempt has been made to simulate the theoretical spillage of thyroglobulin into the circulation by giving rabbits repeated intravenous injections of thyroid extract and following their antibody production. Thirdly, a pilot study has been done to ascertain the possible effects of local trauma to the thyroid gland on antibody production.

Methods

Thyroid extract was prepared according to the method of Witebsky et al. (1955). Thyroids from healthy rabbits were dissected free of fat and connective tissue and frozen on dry ice. The frozen glands were homogenised in a 'Teflon' grinder and extracted with cold isotonic saline for twelve hours. The supernatant, after centrifugation at 3000 r.p.m. for five minutes, was emulsified with equal volumes of Freund's adjuvant.‡ Three experimental procedures were set up.

Experiment I

One group of 18 rabbits was given thyroid extract and Freund's adjuvant containing 0·5 mg. of *Mycobacterium butyricum* ‡ per ml. A second group of 15 rabbits received the mixture containing 2·5 mg. of bacteria per ml. This latter concentration only slightly exceeded that used by Witebsky. The rabbits (weighing 2500 g. equally sexed) were given 0·05 ml. of the above emulsified antigens into each foot pad. Antibody titres were estimated by the tanned-red-cell technique of Boyden (1951) as modified by Stavitsky (1954). Titrations were done at approximately three-weekly intervals on the day after bleeding. The sera were then frozen and re-examined when the animal was killed. At this time all the sera from each animal were tested on one day. No significant differences were noted after long storage. Sera were also tested against different batches of antigen without any significant variation in titre.

Experiment II

12 rabbits were injected intravenously with the saline thyroid extract alone; they received 0·025 ml. (diluted to 0·1 ml.) every two days for four weeks. 2 additional rabbits were given 0·1, 0·2, 0·4, 0·6, and 1·0 ml. of thyroid extract every three days. All these injections were given into the marginal ear vein. Hæmagglutination titres were estimated every six weeks, and the animals were killed after seven months.

Experiment III (Pilot Study)

Physiological saline and Freund's adjuvant with both low and high bacterial concentrations were injected into the right lobe of the thyroid, a separate rabbit being used for each material. Hæmagglutination estimations were done every two weeks and the animals killed at eight weeks when the right and left lobes were dissected and fixed separately in formol saline.

Results

Experiment I

7 of the 18 rabbits which had received the lower bacterial concentration in the Freund's adjuvant exhibited antibody against the thyroid extract. 2 of these rabbits, which displayed a prompt response with titres above 1/4000 at six weeks, were killed three months after initial injection, when the titre was still higher. One of these showed a few focal collections of lymphocytes and plasma cells in the thyroid gland associated with slight follicle damage (fig. 1). 2 further rabbits were killed at six months when the antibody response suggested a maximum. The immunological response of one is shown in fig. 2. In the series of Witebsky, titres of this level were usually

* Fellow National Research Council of Canada.
† Lederle Medical Student Research Assistant.
‡ Difco Laboratories, Detroit, Michigan.

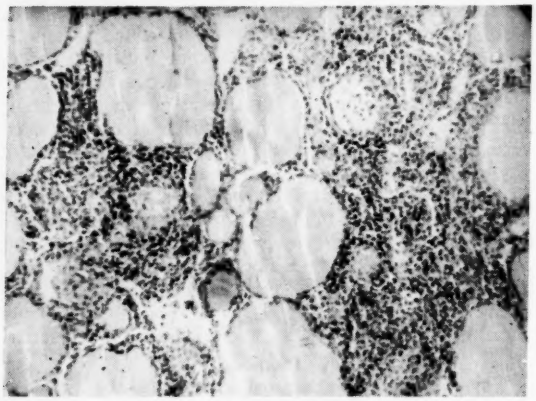


Fig. 1—The only focal area of thyroiditis observed in 1 of the 15 rabbits that developed hæmagglutinating antibodies. This was the only focus of inflammation in the entire gland. (×245. Hæmatoxylin and eosin.)

associated with considerable histological change in the thyroid gland, but in neither of our animals were any unusual features seen. The last 3 animals were followed for one year, and their antibody titres, after reaching a maximum at three to five months, fell gradually (fig. 3) to reach normal (1/16) by eight months. No changes were seen in the thyroids when the animals were killed at twelve months. No thyroid damage was seen in the animals which had shown no antibody response.

11 of the 15 rabbits receiving the higher concentration of *Myco. butyricum* in Freund's adjuvant developed circulating antibody against thyroid extract. 8 of these still showed a significant titre, ranging from 1/128 to 1/4000 when they were killed seven months after inoculation. No significant pathological lesions were found in the thyroids of any of this group, except for a few small foci of lymphocytes in 3.

Experiment II

The rabbits given intravenous injections of thyroid extract showed neither antibody response nor any histological alteration of the thyroid gland.

Experiment III

The injection of saline and Freund's adjuvant into the right lobe of the thyroid had a conspicuous local effect. The gland injected with saline showed a dissolution of the follicular walls with spillage of colloid into the interfollicular tissues, while those that had been injected with the Freund's adjuvant showed complete destruction of the gland architecture and an associated chronic granulomatous reaction with abundant plasma cells and lymphocytes, and some multinucleated giant cells.

In spite of this extensive local thyroid damage, no circulating antibodies were demonstrated in the animals and no pathological lesions could be demonstrated in any of the contralateral thyroid lobes.

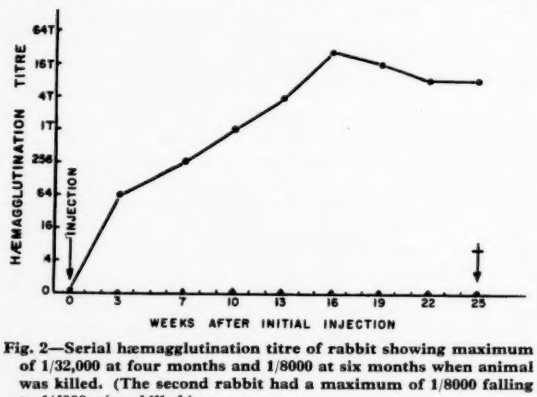


Fig. 2—Serial hæmagglutination titre of rabbit showing maximum of 1/32,000 at four months and 1/8000 at six months when animal was killed. (The second rabbit had a maximum of 1/8000 falling to 1/4000 when killed.)

Discussion

In this experiment on rabbits we have been able to produce, fairly regularly, antibodies against saline thyroid extract when the antigen is emulsified with Freund's adjuvant. The number of animals in which this could be accomplished was related in part to the concentration of the mycobacterium in the adjuvant. The antibody curve was that which could be expected after a single antigenic stimulus. There was no evidence that the immunological reaction was being perpetuated.

No lesions were produced that remotely resembled Hashimoto's thyroiditis. Occasionally small focal collections of lymphocytes were observed, but they were not associated with any follicular alteration and were not considered significant except in one possible instance (fig. 1).

When no adjuvant was used and the saline antigen was injected intravenously no antibody could be demonstrated, although the quantity injected exceeded many times the maximum volume extracted from the thyroid gland of one rabbit. Neither were any thyroid lesions produced. Local severe damage to a single lobe of the thyroid produced neither circulating antibodies nor any lesions in the contralateral lobe.

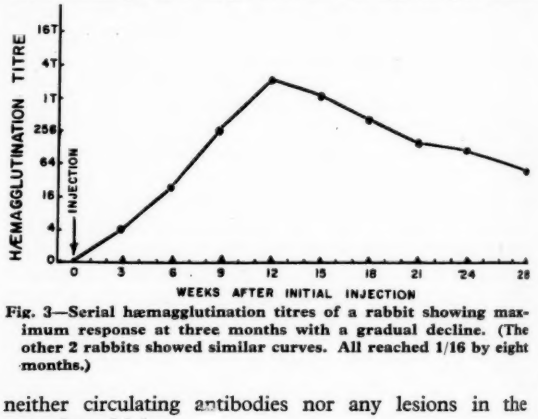


Fig. 3—Serial hæmagglutination titres of a rabbit showing maximum response at three months with a gradual decline. (The other 2 rabbits showed similar curves. All reached 1/16 by eight months.)

The antibodies demonstrable by the hæmagglutination technique in the sera of most patients with Hashimoto's thyroiditis may be a reflection of the pathological change rather than its cause. It has been shown that these antibodies are directed only against the thyroglobulin moiety of the crude thyroid extract.

Trotter et al. (1957), Belyavin and Trotter (1959), and Anderson et al. (1959) have shown that a second antigen-antibody system exists in many of these patients and can be demonstrated only by the complement-fixation reaction. In this system the antigen appears to be an intracellular component, being recovered in the "microsomal" fraction of thyroid homogenates. The highest concentration of this antigen is found in thyrotoxic thyroid glands. It is possible that damage to the thyroid, resulting from an intracellular antigen-antibody reaction involving this system, might be the initiating factor of thyroiditis, and that leakages of antigenic thyroglobulin may then lead to the formation of antibody so readily demonstrated by the hæmagglutination techniques. It seems very doubtful that this latter circulating antibody plays any particular role in compounding further thyroid damage by antigen-antibody union within the acini. One must also recognise the possibility

that some other cytotoxic agent may be involved, as suggested by Pulvertaft et al. (1959) and Irvine (1960).

Our failure to produce thyroid lesions in the rabbit may have been related to the nature of the antigenic material derived by saline extraction from normal thyroids. Since there is some clinical evidence that thyrotoxicosis may precede certain forms of thyroiditis, we are now trying to assess the effect of antigens prepared from experimentally produced hyperplastic rabbit thyroids and antigens prepared by methods other than saline extraction.

Summary

Circulating antibodies, demonstrated by the hæmagglutination technique, have been produced readily in rabbits by injecting them with a homologous antigen obtained by saline extraction of thyroids emulsified with complete Freund's adjuvant. However, no significant lesions were observed, nor were antibodies or lesions produced in other rabbits given the saline extract antigen intravenously. Direct injury of one thyroid lobe failed to produce hæmagglutination antibodies or lesions in the contralateral lobe.

These findings cast considerable doubt on the importance of the hæmagglutinating antibodies in the initiation of thyroiditis or in their compounding further thyroid damage by a self-perpetuating autoimmune mechanism.

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REFERENCES

Anderson, J. R., Gordie, R. B., Gray, K. G. (1959) *Scot. med. J.* **4**, 64.
Belyavin, G., Trotter, W. R. (1959) *Lancet*, i, 648.
Boyden, S. V. (1951) *J. exp. Med.* **93**, 107.
Doniach, D., Roitt, I. M. (1957) *J. clin. Endocrin.* **17**, 1293.
Fromm, G. A., Lascano, E. F., Bur, G. E., Exalante, E. (1953) *Rev. Asoc. méd. argent.* **67**, 62.
Irvine, W. G. (1960) *J. Endocrin.* **20**, 83.
Lancet (1957) i, 1075.
Pulvertaft, R. J. V., Doniach, D., Roitt, I. M. (1959) *Lancet*, ii, 214.
Roitt, I. M., Doniach, D., Campbell, P. N., Vaughan Hudson, E. (1956) *ibid.* i, 820.
Rose, N. R., Witebsky, E. (1956) *J. Immunol.* **76**, 417.
Sommers, S. C., Meissner, W. A. (1954) *Amer. J. clin. Path.* **24**, 434.
Stavitsky, A. B. (1954) *J. Immunol.* **72**, 360.
Stuart, A. E., Allan, W. S. A. (1958) *Lancet*, ii, 1204.
Terplan, K. L., Witebsky, E., Rose, N. R., Paine, J. R., Egan, R. W. (1960) *Amer. J. Path.* **36**, 213.
Trotter, W. R., Belyavin, G., Waddams, A. (1957) *Proc. R. Soc. Med.* **50**, 961.
White, R. G. (1957) *ibid.* p. 953.
Witebsky, E., Rose, N. R., Shulman, S. (1955) *J. Immunol.* **75**, 269.
— — Terplan, K., Paine, J. R., Egan, R. W. (1957) *J. Amer. med. Ass.* **164**, 1439.

NICKEL SENSITIVITY AS A CAUSE OF INFUSION REACTIONS

J. C. STODDART
M.B. Durh., F.F.A. R.C.S.
LATELY REGISTRAR, DEPARTMENT OF ANÆSTHETICS, ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE *

MANY of the cannulæ used for routine intravenous infusions either are nickel-plated or are made of a nickel-containing alloy. In this country alone, many hundreds of infusions are given via such cannulæ daily, but nickel dermatitis from this cause has not been described. The following cases, which were seen in one hospital within three months, suggest that this reaction can occur.

Case-records

Case 1.—A married woman of 35 was admitted for bilateral breast reduction. Her history and the physical examination revealed no abnormality apart from the large breasts. After induction of anæsthesia a plasma infusion was set up, and the patient was placed on the operating-table in a semi-sitting position, with a 20° head-up tilt. 30 minutes later her condition began to deteriorate, and after a further 15 minutes, her systolic blood-pressure was only 40 mm. Hg. Blood, dextran, and finally noradrenaline were given before her condition improved. Only one breast was operated upon because of this incident, and an infusion was continued for about 7 hours after the operation.

Next day, she was quite well, but a generalised urticarial rash with pruriuts developed and persisted for 5 days, despite treatment with anti-histamine drugs. Apart from the rash, she made a good recovery and was discharged home on the 17th postoperative day.

When the rash appeared, the patient told the ward staff that she was nickel-sensitive, but it was not appreciated that she had been in contact with nickel, and the importance of this information was overlooked.

The same patient was admitted 10 days later for operation on the other breast. The course of this operation was uneventful. It was performed with the patient supine and after premedication which included the anti-histamine drug promethazine. She was given two pints of blood during the operation, and the infusion was continued for 4 hours after the operation.

On the second postoperative day, a generalised urticarial rash again developed and persisted for 2 weeks. It was associated for part of this time with angioneurotic œdema of the face and upper limbs. She was discharged on the 21st postoperative day.

Case 2.—A married woman of 23 was admitted as an emergency with a perforated duodenal ulcer. She was given two bottles of plasma before the operation, and a pint of blood during the operation; and intravenous therapy was continued for a further 48 hours. About 8 hours after the operation, she began to feel itching and paræsthesiæ in her hands and feet, but she said nothing about this at the time.

On the first postoperative day, a generalised erythematous rash developed, with small vesicles around the nail-beds of her fingers and toes. She was asked about previous skin rashes, and she said that her doctor had told her she had nickel dermatitis, because she had a local reaction if she wore underwear with metal buckles, or costume jewellery, particularly earrings.

When the infusion was stopped next day, a localised urticarial weal was found corresponding with the exposed part of the hub and shaft of the infusion cannula. This was surrounded by an area of erythema which almost encircled the arm and which itched intensely. The rash subsided in about 5 days, but on discharge from hospital on the 8th postoperative day, the patient still complained of itching between her fingers and toes, and had some minute petechiæ on the palms of her hands.

Investigations

The two types of cannulæ and the metal gauze filter in infusion sets in this hospital, and the cannula in the Capon Heaton disposable infusion set were analysed.

Cannula 1 (obtained locally).—Nickel-steel shaft; brass hub, nickel-plated.

Cannula 2 (obtained from the Ministry of Health).—Nickel-steel shaft; brass hub, nickel-plated.

Cannula 3 (Capon Heaton).—Nickel-steel shaft; plastic hub.

Metal gauze filter.—Nickel 66%, copper 34%.

To confirm that these cannulæ could cause sensitivity reactions, a subject known to be nickel-sensitive was patch-tested with cannulæ 1 and 2. The cannulæ were removed after 24 hours, and 12 hours later, a local eczematous reaction occurred, with erythema, small vesicles, and pruritis. At the same time, the subject became sensitive to the metal parts of her underwear, and developed a reaction at each site.

No history of sensitivity to substances other than nickel could be elicited from either of the above-mentioned patients. Dr. G. Holti, of the department of dermatology, was provided with a list of the substances the patient in case 1 was known to

* Present address: R.A.F. Hospital, Ely, Cambs.

have been in contact with immediately before, during, and after the operations. The list did not include nickel, but included thiopentone, penicillin, streptomycin, cetrimide, 'Phisohex', 'Raytex', 'Hibitane', black silk, and catgut. Negative findings were obtained with all except intradermal cetrimide 0·5%, and Dr. Holti was of the opinion that this positive reaction was of doubtful significance, because there was no reaction where the patient's skin was prepared with cetrimide immediately before the operation.

This patient was later tested for sensitivity to nickel. A prick test with 1% nickel sulphate produced a 4 mm. urticarial weal within 15 minutes. This reaction disappeared during the next hour, but four hours later there was a secondary reaction at the site of the prick test in the form of an urticarial weal, the size of a sixpence (2 cm.), with a "tadpole tail" of œdematous lymphatics leading from it. This reaction was subsiding when the patient went to bed 4 hours later and had disappeared by the next morning, but there was an easily palpable thickening at the site of the prick test 48 hours later. A patch test performed with 1% nickel sulphate produced a local eczematous reaction after 48 hours.

Discussion

Nickel dermatitis is an acquired sensitivity reaction. It was the commonest contact dermatitis in the large series of Marcussen (1959), and its incidence is thought to be increasing (Calnan 1956, Fisher and Shapiro 1956, Marcussen 1959).

Because they are more often in contact with this metal than men, women are more commonly affected. The metal is present in most plated objects and in many alloys, however, and men may also acquire sensitivity to it.

Nickel dermatitis is characterised by a primary eruption at the site of contact, which may be followed by spread to other sites, such as elbow flexures, face, and eyelids. Generalised spread usually takes the form of an eczematous eruption, but angioneurotic œdema, erythema multiforme, urticaria, pruritus, or prurigo may develop (Calnan 1956). If circulating antibodies are present, an anaphylactoid reaction is possible (Holti, personal communication).

Allergic reactions to blood or plasma are said to arise in from 1% (Maunsell 1944, Hoxworth and Skinner 1941, Seldon 1956) to 3% (Stephen et al. 1956) of infusions. Maunsell concluded that this type of reaction was due to sensitivity of the recipient and not to the blood or plasma infused. Discombe (1958) stated that allergic reactions arose in from 2% to 8% of infusions, and he described an anaphylactoid non-hæmolytic reaction of unknown cause.

The cases described may be regarded as examples of nickel sensitivity, the generalised spread being due to the introduction of nickel into the circulation. In one patient, there was also a typical local reaction. In the other patient, this was not looked for. The collapse of the first patient may have been an anaphylactoid reaction to nickel, and the immediate reaction to the prick test makes this probable. There are, however, other possible causes for this episode—particularly reduced venous return due to the patient's position. Electrocardiography, chest X-ray, urine microscopy, and spectroscopy were normal.

Perhaps the most likely alternative cause of the rashes in these cases is an allergic reaction to the blood or plasma infused, and this cannot be excluded. There was no evidence of incompatibility, however, with the blood infused. Reactions to blood or plasma usually take the form of rigors and pyrexia; if skin reactions occur, they usually do so either during the infusion or within 2 hours of it, and do not persist for more than 6 hours (Maunsell 1944, Stephen et al. 1955, Griffitts and Elliott 1955, Seldon 1956, Discombe 1958). If the collapse of the first patient is disregarded, the first symptom of a reaction did not occur until 8 hours after the blood transfusion was stopped; in the other case, the interval was 18 hours on the first occasion, and 36 hours on the second occasion.

Summary

Skin reactions developed in 2 patients who had had infusions, and in 1 of these there was also an alarming anaphylactoid reaction. It is suggested that the cause was sensitivity to the nickel in the infusion cannulæ. As nickel sensitivity is relatively common, a proportion of the hitherto unexplained infusion reactions may be due to nickel cannulæ, which may produce manifestations of the immediate or delayed type of hypersensitivity.

I wish to thank Dr. G. Holti for his very helpful advice, and for performing the skin tests on the first patient. I should also like to thank Dr. J. A. Gilchrist, of the department of metallurgy, King's College, Newcastle upon Tyne, for performing the analyses, Dr. M. H. A. Davidson and Dr. D. C. C. Stark for referring case 1 to me, and Prof. E. A. Pask and Prof. C. A. Green for their encouragement.

REFERENCES

Calnan, C. D. (1956) *Brit. J. Derm.* **68**, 229.
Discombe, G. (1958) *Acta hæmat.* **20**, 210.
Fisher, A. A., Shapiro, A. (1956) *J. Amer med. Ass.* **161**, 717.
Griffitts, J. J., Elliott, J. (1955) *Curr. Res. Anesth. Analg.* **10**, 290.
Hoxworth, P., Skinner, C. (1941) *Arch. Surg. Chicago*, **42**, 321.
Marcussen, P. V. (1959) *Brit. J. Derm.* **71**, 97.
Maunsell, K. (1944) *Brit. med. J.* ii, 236.
Seldon, T. H. (1956) *Med. Clin. N. Amer.* **40**, 1217.
Stephen, C. R., Martin, R. C., Bourgeois-Gavardin, M. (1955) *J. Amer. med. Ass.* **158**, 525.

FATAL RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

DEREK L. PRYER
M.B. Lond., F.F.A. R.C.S.
SENIOR ANÆSTHETIC REGISTRAR

RICHARD R. L. PRYER
M.B. Lond., F.R.C.S.
CONSULTANT SURGEON

ANN F. WILLIAMS
M.B. Dubl.
ANÆSTHETIC REGISTRAR

AYLESBURY HOSPITAL GROUP

DEFECTS in the cuffs of endotracheal tubes are an occasional cause of respiratory obstruction. Incidents described include the herniation of part of the cuff over the open end of the tube (Forrester 1959) and herniation of the cuff into the lumen of an armoured tube (Robbie and Pearce 1959).

We now report another possible mechanism underlying this type of accident.

Case-report

A healthy woman, aged 33, was admitted to hospital for the removal of a moderate-sized, non-toxic, nodular goitre. X-rays of the chest and neck revealed no evidence of tracheal displacement or narrowing.

Premedication was with 10 mg. morphine and 0·6 mg. atropine one hour preoperatively.

Anæsthesia (A. F. W.).—Induction was with thiopentone sodium 375 mg. and succinyl choline 70 mg. The lungs were inflated with oxygen, the vocal cords and trachea were sprayed

with 4 ml. of 4% lignocaine, and the patient was then intubated with a no. 8 Magill cuffed endotracheal tube. The cuff was inflated immediately before use, and appeared to be in good condition. Following intubation, the cuff was again distended with air from a syringe. Filling was judged to be adequate when leakage of air past the cuff just ceased on inflation of the lungs. Anæsthesia was maintained with nitrous oxide and oxygen (6:2 litres per minute) on a semi-open circuit, and respiration was controlled. Full spontaneous respiration returned after a few minutes, and the patient was then transferred to the operating-theatre.

Infiltration of the superficial tissues in the operation field was carried out, using 80 ml. of a solution containing 400 mg. lignocaine and 0·5 mg. adrenaline in 160 ml. of physiological saline. Before the incision was made the patient was given 15 mg. of tubocurarine chloride, and thereafter respiration was assisted.

The operation (R. R. L. P.) proceeded uneventfully until the point when the partial resection of both lobes of the thyroid was about to start. At this moment the anæsthetist was suddenly unable to inflate the lungs. Thinking that the tube might have become incorrectly placed, she adjusted its position, with no result. All surgical instruments were removed from the wound to exclude the possibility of tracheal compression at this site. Head towels were then removed, revealing that the patient was deeply cyanosed. Laryngoscopy was performed, and kinking of the tube excluded. The cuff was deflated, and a suction catheter was passed; and, although no mucus was obtained, the airway was restored after this manœuvre.

At this juncture the lungs were inflated with pure oxygen, without improvement in the patient's colour. The pulses were examined, but could not be felt, and the pupils were found to be widely dilated.

An intracardiac injection of adrenaline was given, without effect.

Transthoracic cardiac massage was performed through an anterior incision in the fifth left intercostal space. The heart was found to be arrested in diastole. After 30 seconds of massage, contractions began, and normal rhythm returned rapidly. Inflation with oxygen was continued throughout this period; and, with the return of the pulse, the patient's colour reverted to normal. 20 minutes later the pupils had contracted symmetrically, and shortly afterwards spontaneous respiration restarted. The blood-pressure remained low, but recovered after infusion of 540 ml. of ' Intradex ' (6% dextran in physiological saline). Thyroidectomy was then completed, after which the thoracotomy incision was closed. At the end of the operation the patient was returned to the ward.

Postoperative course.—At this time, respiration was full and spontaneous, and the pulse, colour, and blood-pressure seemed satisfactory. The patient appeared lightly unconscious, making crying noises, and apparently resenting painful stimulation. Twitching movements of her face were noted.

During the next 6 hours the level of unconsciousness slowly deepened, twitching of the face and limbs became more prominent, and the pupils dilated progressively. As these signs indicated anoxic cerebral damage, measures were taken to combat the associated cerebral œdema. Intravenous administration of 50% sucrose (Argent and Cope 1956) and concentrated plasma, with pressor drugs (methylamphetamine and methoxamine), failed to produce any notable effect, and the patient died in coma 6 hours after leaving the theatre.

The Endotracheal Tube

After the operation one of us (D. L. P.), who had been in an adjacent theatre, and had been sent for when the respiratory obstruction developed, examined the endotracheal tube and found that the cuff inflated unevenly. There was an obvious localised balloon-like protrusion which had developed at a presumed point of weakness in the most distal part of the cuff. This was located on the aspect of the cuff which lay behind the bevel of the tube. As the tube was known to be normal when inserted, the possibility was considered that this protrusion had occurred during the operation, and had forced the bevelled open end of the tube against the tracheal wall, thereby occluding the airway.

Necropsy (Dr. H. J. Harris).—This showed the cause of death to be cerebral anoxia due to respiratory obstruction and cardiac arrest.

At the postmortem examination, the endotracheal tube used for the anæsthetic was inserted, with the patient's body placed in the extended-neck position adopted at operation. By opening the trachea longitudinally, it was possible to observe the exact position of the tube. It was found to be correctly placed, with the tip 1 in. above the carina. The open bevelled end was observed to face anteriorly. Inflation of the

Diagrammatic representation of findings at necropsy experiment.

defective cuff resulted in the open end of the tube being forced firmly against the front of the trachea (see figure). The appearances suggested to those present that this would have resulted in complete obstruction of the tube at operation.

Comments

We make the following comments after considering the episode described:

1. Uneven inflation of cuffs, as a result of weakness in the rubber or perishing during storage, is found fairly frequently when large numbers of stored tubes are examined. In the operating-theatre where the episode described here took place, all endotracheal tubes are examined, and the cuffs inflated weekly by the theatre superintendent, faulty ones being rejected. In addition, each tube is inflated and tested by the anæsthetist before use. Despite these precautions, it was possible for a defect to develop suddenly, while the tube was in use, with the results described. This emphasises the importance of discarding any tube where the least suspicion of weakness or uneven inflation exists.

2. It is understandable that, where an anæsthetist employs an endotracheal tube with the express purpose of avoiding respiratory obstruction, he may fail to consider that a defect in the device itself may produce the very complication that he seeks to avoid. Should obstruction develop, he is likely to consider other possibilities first. As this incident shows, such delay may prove fatal. We therefore draw attention to this possibility, and suggest that, where possible, immediate or early deflation of the cuff should be practised in such circumstances.

3. It is often stated that, when cardiac arrest occurs, a period of about 4 minutes elapses, at room-temperature, before irreversible anoxic damage takes place in the brain. Some have suggested that part of this period may be spent in attempting less radical measures to restore the heart action, before undertaking cardiac massage. But many would dispute the advisability of any immediate measure short of cardiac massage.

Where cardiac arrest is secondary to respiratory obstruction, the brain is already anoxic; and the assumption that any safe margin of time exists is invalid. No time should be lost in starting cardiac massage, as this is undoubtedly the most effective way of restarting the pulse.

REFERENCES

Argent, D. E., Cope, D. H. P. (1956) *Brit. med. J.* i, 593.
Forrester, A. C. (1959) *Anæsthesia*, **14**, 388.
Robbie, D. S., Pearce, D. J. (1959) *ibid.* p. 379.

Reviews of Books

Intussusception in Infants and Children

MARK M. RAVITCH, M.D., associate professor of surgery, Johns Hopkins University School of Medicine, and surgeon-in-chief, Baltimore City Hospitals. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 119. 76*s*.

THIS monograph is based on twenty years' experience with the reduction of intussusception by hydrostatic pressure in the Harriet Lane Home of the Johns Hopkins Hospital. It is clear from the figures Dr. Ravitch gives that intussusception is probably more common in some of the pædiatric surgical centres of Great Britain and Europe than in those of the United States. In the Harriet Lane Home 199 intussusceptions have been treated between 1893 and 1958 and the mortality has fallen from 75% to nil in the years 1948 to 1958, while the average duration of symptoms has fallen from fifty-six hours to twenty-five hours in the ten years up to 1958. From 1893 to 1948 only 4 children died out of 52 treated within twenty-four hours of the onset of symptoms. In 1876 Hirschsprung of Copenhagen reported the use of hydrostatic pressure in the treatment of 107 patients with intussusception with a mortality-rate of 35% when the general mortality from the disease was 80%; in the 84 cases he treated with enemas alone the mortality was 23%. In 1926 Hipsley of Sydney was able to report 100 patients treated by saline enemata with only 5 deaths. Between 1939 and 1957 reduction by barium enema has been attempted by the Harriet Lane Home in 77 patients and has succeeded in 53, but operation was judged advisable in the remaining 24, in 5 of whom the intussusception was found to be reduced completely, and in 18 it has been pushed back to the cæcum. Reducibility by enema was not related to the position of the apex at the time of diagnosis. None of these 77 patients died.

There is a good description of the technique of reduction by enema and of the precautions which should be observed. It is obvious that a limit must be set to the duration of the procedure and while some intussusceptions may be reduced in a few minutes others may persist even after three-quarters of an hour. The image-intensifier is likely to make this method of treating intussusceptions more readily applicable than before and the results of this method in some centres in North America and Australia clearly demand respect. There are few hospitals in this country which have achieved such low mortality-rates by operation alone and it seems as if surgeons and especially pædiatric surgeons must think again about their methods of treating intussusception—and they should all read this book.

Safe Handling of Radioactive Isotopes in Medical Practice

EDITH H. QUIMBY, SC.D., professor of radiology (physics), College of Physicians and Surgeons, Columbia University. New York. New York and London: Macmillan Company of New York. 1960. Pp. 129. 31*s*. 6*d*.

OFFICIAL codes of practice governing the use of radioactive isotopes in hospitals in this country and in the United States and the guide issued by the International Atomic Energy Agency all prescribe the appointment of a radiation protection officer who is expected to draw up detailed working rules for his hospital and to deal with day-to-day difficulties or emergencies. Professor Quimby seeks to ease his task by providing enough background information to enable the people concerned, notably technicians and nurses, to appreciate the reasons for the detailed rules which they are expected to follow.

Introductory chapters on radioactivity and its measurement, the nature of radiation hazards with particular reference to isotope work, and the main clinical uses of radioactive materials, deal briefly with their complex subject matter yet remain readable, clear, and informative. Other chapters describe in detail various practical problems, illustrated where appropriate with numerical examples. The radiation protection officer himself will find it a practical reference book when dealing with queries which may lie outside his own experience. With the help of the excellent index he can, for instance, quickly find the answer to such questions as the possible hazard to the fœtus if a pregnant nurse is looking after a radioactive patient or the possible risks faced by the "funeral director" who may be dealing with a radioactive corpse. It will also be a useful guide for anyone who has the difficult task of giving some elementary lectures on this subject. Indeed, Professor Quimby has succeeded so well in presenting a great deal of information in a form which can be understood by a non-specialist that it is particularly unfortunate that the price of her small book is so high as to put it out of the reach of most of the people for whom it is intended.

Diseases of the Newborn

ALEXANDER J. SCHAFFER, M.D., associate professor of pediatrics, Johns Hopkins Medical School; pediatrician to Johns Hopkins Hospital. Philadelphia and London: W. B. Saunders. 1960. Pp. 878. 140*s*.

THE medical management of the newborn is challenging and exciting—challenging because of the variety of disorders met in this hazardous period, and exciting because the physical status of the patient is unknown until the first examination. Dr. Schaffer writes with the interest and enthusiasm of one who has accepted the challenge and felt the excitement. With the exception of the section on cardiac disease (by Dr. M. Markowitz), it is a personal book and is all the better for that.

He puts the emphasis on diagnosis and treatment and does not wander down the pathways of fœtal and neonatal physiology unless he is clinically compelled to do so. The authority of the book derives from his wide experience and selective reading and his rich gathering of illustrative cases. Though his book is not encyclopædic he describes helpfully most conditions affecting the newborn. The balance between rare and common conditions is more suitable for the practising doctor than the medical student. The references, mostly from American or British sources, have been sensibly chosen from among the readily available rather than the most academic.

One day a multi-authored, comprehensive, and probably unreadable book will appear on the newborn infant. Some pædiatricians and some libraries will prefer it, but Dr. Schaffer need have no regrets; for his book, which he has obviously enjoyed writing, will already have won its own permanent place.

Relaxation for Childbirth. (London: Heinemann Medical Books. 1960. Pp. 148. 12*s*. 6*d*.).—Instruction in controlled relaxation during labour has helped many mothers both physically and mentally, not only during childbirth itself but also during pregnancy and later. Miss Mary Barfield found her courses of instruction to expectant mothers so successful that she thought her methods might help others out of reach of classes—so she wrote this book. She has chosen to write just as she speaks to the mothers, and the result often seems rambling, making it difficult to look anything up. But anyone who is undaunted by this will find here, with one omission, the important details about relaxation in childbirth. The omission is a discussion of the vital difference between attending a course in "natural childbirth" and reading a book about it. Relaxation during labour is extremely hard for most women to achieve: even those who can relax easily under normal conditions often find it impossible in the presence of extreme discomfort (in the language of "natural childbirth" the word "pain" is not allowed). There are a few lucky women to whom relaxation during childbirth comes naturally, either with or without training; but most Western women require long training, attendance at classes, and often the devoted services of an expert during the actual labour. Such women are unlikely to be successful simply from reading a book. Miss Barfield's text contains many ecstatic descriptions of motherhood, but it does not discuss the less radiant side of the picture. Women who suffer a lot despite or even because of "training" in relaxation may not let Miss Barfield know how they feel—but they have plenty to say to the doctor who attends them.

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Perchance to Dream

IN olden times dreams and their interpretation played a large part in statecraft, and the decline in such use has left our political scene the duller. Latterly the classic work of FREUD [1] on dream interpretation, first published some sixty years ago, laid the foundations of psychoanalysis; and, with a different approach, J. W. DUNNE,[2] the philosopher and mathematician, used dreams for time experiments. DUNNE'S conclusion that subsequent events could be recognised in preceding dreams was based on a good deal more evidence than is often realised: with the rise of extrasensory perception as a respectable subject, his careful work merits a second look. Unfortunately, owing to the subjective, elusive, and unrepeatable nature of dreams, scientific control of their investigation has proved difficult, though EYSENCK [3] reported an interesting technique: an imaginary episode, implanted in a volunteer under hypnosis and banished to posthypnotic amnesia, was followed by a very relevant dream packed with Freudian symbolism.

A new and promising line has been opened up by DEMENT,[4] of Mount Sinai Hospital, New York. Starting from the observation that dreams were accompanied by rapid synchronous eye movements (probably as the dreamer "watched" the events of the dream) he studied dream cycles by means of electroencephalograms (E.E.G.) and electrical records of eye movements. A typical night of undisturbed sleep was found to include four or five periods of dreaming, each lasting some twenty minutes and accompanied by lightening of sleep, shown on the E.E.G. In an effort to establish how far this dream experience (equal to about 20% of the total sleep-time) was physiologically necessary, dreaming was abolished: for five successive nights as soon as eye movements and E.E.G.s suggested the start of a dream cycle, the eight volunteers (all were young men) were firmly woken up. On the first night this awakening was followed by a normal dreamless spell; but the pressure of dreaming increased and more and more frequent awakening was required on subsequent nights. Practical difficulties prevented total dream deprivation, and DEMENT estimates that the dream loss was 65–75%. During the first of the subsequent "recovery" nights of undisturbed sleep, six of the eight volunteers dreamed some 50% in excess of normal; one subject dreamed normally on the first recovery night (after a cocktail party) but excessively on the following four nights; only one did not over-dream. Compensatory over-dreaming lasted for about five nights—i.e., about the same time as the preceding deprivation. That this result was due to deprivation of dreams rather than of sleep was suggested by a further series of recordings in which six of the subjects were similarly awakened for the same number of nights but not during dreams: thereafter the increase in dream-time was much smaller. During dream deprivation the subjects became anxious and irritable and their mental concentration poor: one subject left the study in apparent panic after three nights and two others stopped short at four nights; five had a greatly increased appetite and gained weight. All these changes disappeared when the dreaming was restored. There were no such changes during the "control" awakenings. The volunteers for this study must have reflected that Macbeth was not the only one who murdered sleep.

These results would have been no surprise to FREUD, who held that "dream-work" was a vitally important part of mental function. An impressive case has been made for regarding dreaming as a basic human need. More important: DEMENT has evolved a new technique for the study of the mind which opens a long row of doors. Physical and mental illness, drugs, personality, age, sex, and cultural background are obvious variables to be correlated with dream patterns; and this work may lead to really valid means of analysing dream content.

1. Freud, S. The Interpretation of Dreams.
2. Dunne, J. W. An Experiment with Time. London, 1927.
3. Eysenck, H. J. Sense and Nonsense in Psychology. London, 1958.
4. Dement, W. *Science*, 1960, **131**, 1705.

Diagnosis of Diabetes

AT present diabetes mellitus is usually diagnosed when the patient reports with symptoms due to the primary disorder or, in about 20% of cases, to complications of the disease.[1] Less commonly cases are discovered incidentally by routine testing of the urine. REID [2] found that 48% of 352 diabetics he studied in Dundee had had symptoms continuously for more than four months when they were diagnosed and 20% had had symptoms for more than a year. Such a state of affairs would no longer be tolerated for tuberculosis, and should no longer be tolerated for diabetes. In tuberculosis infectivity is an important factor, but delay in the diagnosis of diabetes can be serious enough. It involves needless suffering and impaired efficiency which may cost the patient his job, increases the severity of the diabetes, and favours the development of complication such as cataract. Some of the delay in diagnosis is doubtless due to imperfections in the practice of doctors who fail to test the urine when the clinical picture suggests diabetes, but much is due to ignorance among the lay public. There is a widespread tendency to misinterpret the symptoms of this disease. Polyuria and visual impairment, for instance, may be regarded as inevitable concomitants of senescence; and loss of weight may be welcomed, particularly by the obese postmenopausal women in whom diabetes is especially liable to develop: in REID'S series long delay in diagnosis was about twice as common in women as in men. Thirst may sometimes be credited with a healthy significance, and pruritus vulvæ may not be mentioned

1. Beaser, S. B. *New Engl. J. Med.* 1948, **229**, 765.
2. Reid, J. J. A. *Med. Offr*, 1960, **103**, 325.

because of embarrassment. REID revealed the depths of lay ignorance about diabetes in a pilot survey of 250 people attending a chest clinic, who were asked to fill in a simple questionary. 78% could express no opinion about the cause of diabetes, and 28% were not sure whether or not it was infective. 69% did not know one symptom of diabetes or of its complications, and only 5% knew two or more symptoms. 28% did not know whether or not treatment of diabetes is successful—a fact relevant to the delay in reporting symptoms when their significance is recognised. The little knowledge of diabetes in this group was derived mainly from conversations with diabetic relatives or acquaintances rather than from reading, the radio, or television.

A resolute effort is needed to lessen this ignorance. Since 1–2% of the population are diabetic [3]—about half of them unknowingly [4]—it seems reasonable that simple instruction in the symptoms of the disease and their significance should be given not only through mass media of publicity but as part of instruction in biology in schools. This disease can now be diagnosed in the latent phase or even earlier—that is, in the prediabetic phase. If the doctor recognises clinical pointers to the disease, then latent diabetes may be revealed by tests of carbohydrate tolerance; and if such tests are at first normal, prediabetes may be revealed by their repetition after administration of cortisone or other glucocorticoids.[5–7] Clinical pointers include a strong family history of diabetes, especially in the elderly and obese; transient glycosuria during stress; the production of excessively large babies or stillborn babies with hyperplasia of the pancreatic islets; and repeated miscarriages or toxæmia of pregnancy, excessive maternal weight-gain during pregnancy often associated with excessive lactation, or congenital malformations in the offspring.[8] By such means the diagnosis of diabetes may be made to antedate by many years the appearance of the overt disorder. In this phase correction of obesity [9] and possibly administration of hypoglycæmic sulphonylureas to stimulate hyperplasia of the insulin-producing β-cells of the pancreatic islets [10] may do much to delay or avert frank diabetes.

Cyclical Œdema and Shock

INCREASED permeability of the capillary wall to plasma-protein is a common cause of local œdema in inflammatory and allergic states; but generalised œdema due to loss of protein through the walls of capillaries throughout the body must be extremely rare. Leakage of protein through the capillaries of particular organs (as in the protein-losing kidney [11] or protein-losing gastroenteropathy [12]) produces effects which are drastic enough; but when such losses take place throughout the body they must cause not merely a hypoproteinæmic œdema but profound and dangerous oligæmic shock. From New York we now have a report,[13] remarkable both for the rarity of the circumstances and the thoroughness with which they were investigated, of a patient who had many episodes of œdema associated with shock, the last of which proved fatal.

A previously healthy married woman of 32 had an attack of generalised swelling, associated with nausea and vomiting, which lasted for a few days. Similar attacks recurred after intervals of 5 and 8 months, but thereafter they became more frequent, and 20 attacks were observed over a 2-year period. In a typical severe attack with shock, of which there were nine, the onset was with malaise, chilliness, and a temperature raised to 39·3°C (102·7°F). The blood-pressure fell from normal levels to 30/0 mm. Hg, and could be raised by amounts of plasma ranging from 500 to 3300 ml. Clinically detectable œdema was present in only some of the attacks, but in all of them the patient gained several kilogrammes in weight. Death in the last attack was sudden; and at necropsy the lungs were œdematous, but there was no embolism. The attacks were related in time to the menstrual cycle, usually just preceding the menstrual flow but occasionally starting a day or two later. This time relation was so striking that after several life-threatening attacks the uterus and later the ovaries were removed. Thereafter the frequency of attacks decreased only temporarily.

Many investigations were made; some were directed towards showing that the attacks were associated with widespread increase in capillary permeability (these were unequivocally positive); others were directed towards finding the cause of the abnormal permeability (these yielded no definite conclusion, but ruled out several reasonable hypotheses). There is the circumstantial evidence that the hæmatocrit percentage was increased in the attacks, during which the infusion of plasma raised the blood-pressure and restored adequate circulation. Other evidence of increased capillary permeability in the attacks was afforded by serial estimates of plasma-volume, and by the disappearance curves of Evans-blue and radioactive iodinated serum-albumin. The full panorama of essentially negative evidence as to the cause of the abnormal permeability must be sought in the original paper. There was indeed some evidence of a vasodilator substance in serum; there was a small amount of an abnormal macroglobulin; and there was an increased amount of heparin-precipitable protein. But the search for an allergen was unrewarded, and there was no response to steroids or anti-histamines. The possibility that endometrial products were gaining access to the circulation and affecting the capillaries was excluded by the failure of hysterectomy to control the attacks; and the subsequent oophorectomy similarly excluded absolute dependence of the attacks on ovarian function. Apparently the effect of vasopressin on the attacks was not observed, and the urine was not tested for hydroxyindole-acetic acid;

3. Walker, J. B. *Post Grad. med. J.* 1959, **35**, 302.
4. Conn, J. W. *Diabetes*, 1958, **7**, 347.
5. Fajans, S. S., Conn, J. W. *Diabetes*, 1954, **3**, 296.
6. Duncan, L. J. P. *Quart. J. exp. Physiol.* 1956, **41**, 453.
7. Goto, Y., Kato, J., Takanami, A., Ohneda, A. *Lancet*, Aug. 27, 1960, p. 461.
8. Jackson, W. P. U. *Post Grad. med. J.* 1959, **35**, 287.
9. Newburgh, L. H., Conn, J. W. *J. Amer. med. Ass.* 1939, **112**, 7.
10. Ashworth, M. A., Haist, R. E. *Canad. med. Ass. J.* 1956, **74**, 975.
11. Platt, R. *Lancet*, 1959, i, 159.
12. Gordon, R. S. *ibid.* p. 325.
13. Clarkson, B., Thompson, D., Horwith, M., Luckey, E. H. *Amer. J. Med.* 1960, **29**, 193.

otherwise everything conceivable seems to have been done, with the conclusion: " The reason for the sudden marked alteration in capillary permeability is unknown, as is the reason for its consistent occurrence during the premenstrual phase of her menstrual cycle."

The relation between the menstrual cycle and systemic disease has been reviewed by ROGERS [14]; the weight-gain in the premenstrual phase is due to salt and water retention rather than to any change in capillary permeability. In this patient fluid retention may have determined the timing of the attacks, but cannot have been their primary cause. Less spectacular episodes of cyclical œdema are known to be far commoner in women than in men, and usually disappear after the menopause.[15] Psychological factors have been shown to influence fluid balance in healthy people,[16] and even in patients with congestive heart-failure [17]; and their importance is well recognised in premenstrual cyclic œdema.[15] Such factors cannot be easily dismissed in a patient with successive near-fatal crises; but it is one thing to recognise their importance, and quite another to say what they are or how they could act.

Although this sad story is not likely to be heard very often we have given it extensive notice, partly because the recorded observations may help in understanding any similar cases and partly because, despite its apparent uniqueness, this record may have some general application. An increase in capillary permeability has at times been postulated as a major factor in the œdema of cardiac failure or of acute nephritis. Because of the complete dissimilarity between such states and the dramatic episodes in this patient (which were demonstrably due to increased capillary permeability) it seems unlikely that cardiac and nephritic œdema are largely due to abnormal capillary permeability—a view which accords with the low protein content of œdema fluid in patients with heart-failure or nephritis.[18]

14. Rogers, J. *New Engl. J. Med.* 1958, **259**, 676.
15. Thorn, G. W. *Amer. J. Med.* 1957, **23**, 507.
16. Schottstaedt, W. W., Pinsky, R. H., Mackler, D., Wolf, S. *ibid.* 1958, **25**, 248.
17. Barnes, R., Schottstaedt, W. W. *ibid.* 1960, **29**, 217.
18. Warren, J. V., Stead, E. A. *Amer. J. med. Sci.* 1944, **208**, 618.

Annotations

STUDENT AND FAMILY

THE system whereby medical students see nothing of patients during the first two or three years of their course is neither eternal nor universal. Our forefathers often started their studies by going as apprentice to a practitioner, while in France the student may be allowed into the wards as soon as he starts training. On the best ways of learning to swim, in medicine as in everything else, there will always be argument; but opinion is now turning against those who believe in several years' instruction before the student gets a sight of the water. One of the ways in which some medical schools try to maintain his initial interest, and direct it usefully, is by giving him personal charge of a family, with which he may remain in touch throughout the years of his medical course.

As will be seen from his article on p. 957, Professor Prasad puts his trust in such a scheme as a means of recalling students from the artificialities of hospital medicine to the reality of daily life. In practice, however, the Indian innovators might avoid some obstacles by studying American schools where, with similar objectives, such schemes have been tried with many different variants. At Western Reserve the family study starts very early in the student's career, when he is present at a birth and afterwards takes an interest in the baby's development.[1] From the child his interest spreads logically to the parents, and so to the other children, whom he visits at home, more or less frequently, during the next few years; and at best this may be an invaluable piece of experience, introducing him to many different medical and social problems and reminding him always that people are people. On the other hand, compared with the traditional doctor-patient relationship, the student-patient relationship is somewhat artificial, and can be awkward: the student may either settle down as a friend of the family (a role by no means to be despised) or he may attempt too much with too little knowledge. Professor Prasad regards the preclinical student as insufficiently mature for such studies. On the other hand, in the comprehensive care and teaching programme under Professer Reader at Cornell University,[2] where they come later in the curriculum, some students (perhaps because they are already in their fourth year) are not happy unless their task is regularised on conventional lines, with non-medical problems docketed for separate attention by the social worker. Though others throw themselves into all the family difficulties, some critics have held that " exposure to overly complicated familial difficulties of patients have turned out to be more detrimental than helpful for certain students at the fourth-year level, allowing them to learn little of the possibilities of comprehensive care, but only of the limitations ".[3] Some American schools defer this kind of practical social teaching until the later stages of the curriculum: their home-care programmes allow the student to take charge of a family, with full support from the hospital, at a time when he is already all but a doctor. In many American schools, of course, social experience is still obtained in the traditional way by sending the students to work with " preceptors " in private practice.

Another scheme which Professor Prasad describes is the allocation of tuberculous families to fourth-year students, who make a study of the whole situation and write it up. Such projects are becoming commoner as a valuable part of medical education, and the student's critical study of a family, culminating in a report on one of its aspects, is perhaps the high spot of the clerkship in environmental medicine and community health now given at the State University of New York. Just as Professor Prasad has found it wise to construct a schedule of study, so Prof. Duncan Clark and his colleagues at the Downstate Medical Center in New York have used a specimen draft, so that students need not be inhibited by having to think out the way in which their report shall be written. But in New York, as in Lucknow, quite a proportion of students turn to this work with real enthusiasm and sit up half the night writing illustrated notes of their observations. Their comments on the action to be taken show that, unlike the majority of doctors in practice, the students of a modern American school are " psychologically oriented ".

1. Pemberton, J. *Lancet*, 1953, ii, 469.
2. Merton, R. K. Reader, G. C., Kendall, P. L. The Student Physician. Harvard University Press, 1957.
3. Goss, M. E. W. *ibid*, p. 249.

Another useful means of teaching these senior students is a discussion of what was done for the patient, with an invitation to them to discover what was *not* done.

PROGNOSIS IN MITRAL STENOSIS

THE sustained efficacy of mitral valvotomy is recognised,[1–3] but the long-term results should be compared with those of medical treatment only. An excellent retrospective study from the era before valvotomy has been made by Rowe et al.,[4] who followed 250 patients (194 women and 96 men) with mitral stenosis until death or for at least ten years; 115 of the patients were followed for twenty years. The cases were divided into four grades of severity at the time of the initial examination: grade 1, no symptoms and normal rhythm; grade 2, mild symptoms with or without atrial fibrillation; grade 3, moderately severe symptoms with or without a major complication; grade 4, chronic heart-failure.

During the first ten years the mortality was highest in the first five-year period, except in the symptom-free group. Of the entire series 61% lived for ten years (84% in grade 1, 42% in grade 2, 15% in grade 3, and none in grade 4). At the end of ten years 40% of the whole series had remained unchanged, 20% had progressed to greater severity, and 40% had died. The cause of death was known in 110 patients, 67 of whom succumbed to progressive heart-failure, 21 to arterial embolism (usually cerebral), 10 to pulmonary embolism, and 5 to subacute bacterial endocarditis before the introduction of antibiotics. Of the 21 who died from arterial embolism 19 were women.

In the 250 patients during the first ten years the prevalence of dyspnœa, pulmonary œdema, congestive heart-failure, atrial fibrillation, arterial embolism, and pulmonary embolism all increased, but oddly enough the prevalence of hæmoptysis remained at 9%. When the patients were first seen 20% had atrial fibrillation, and the proportion increased to 33% at the end of the ten years. During the ten-year period 30 patients, nearly all with atrial fibrillation, had 48 episodes of systemic embolism. Associated systemic hypertension was present in only 6%.

Of the 115 patients whose fate was known after twenty years, 43% were originally classified as grade 1, 45% as grade 2, and 12% as grade 3, in contrast to the original 250 patients, with 52%, 37%, and 10% in these three grades respectively. 45% were still alive in the eleventh year, 30% in the fifteenth year, and 21% at the end of twenty years. 40% of patients in grade 1 survived the full twenty years, but only 8% in grades 2 and 3. Major symptoms and complications increased with time as in the ten-year group, but pulmonary œdema and congestive heart-failure were more frequent than in the ten-year group. Arterial embolism occurred in 26% of the 115 patients, again almost exclusively in women.

Rowe et al.[4] compared these results with those in other series. The results were very similar to those reported by Grant,[5] who described the course of mitral stenosis over a ten-year period in 238 men. More recently, Olesen[6] reviewed 271 patients with dominant mitral stenosis. The severity of the disease and ages of the patients were greater than in Rowe's[4] group; and this was reflected in a ten-year survival of only 35%, compared with 61%.

Comparison of the survival curves of the three medical series with the surgical series of Ellis et al.,[7] followed for seven years after valvotomy, reveals appreciable differences. 90% of the surgically treated patients were alive at the end of seven years, compared with only 60% of the composite medical series of 759 patients, and 45% of Rowe's[4] series of 250 patients. The superiority of surgical over medical treatment for critical mitral stenosis is borne out by Donzelot et al.[8] 157 patients with mitral stenosis treated medically were followed for from twenty months to five years, during which time 71 died and 45 others became worse: none improved. By contrast, of 165 patients who were operated on, 133 improved, 14 did not change, 2 became worse, and 16 died. Admittedly, as 120 of the patients treated medically were considered unsuitable for valvotomy owing to associated lesions or irreversible heart-failure, the comparison is not strictly fair; but of 19 other patients who were all advised to undergo valvotomy but refused, 11 died within five years, 4 deteriorated seriously, and only 4 did not become worse. This experience agrees with that of Harken et al.,[9] who reported that 17 of 19 patients died within a year of refusing valvotomy.

Mitral valvotomy thus appreciably improves the long-term outlook of mitral stenosis, and the immediate good results are usually maintained. The data of Rowe et al. suggest that without surgical aid a patient with significant mitral stenosis who has symptoms when first seen has a probability of death by the end of ten years, and a strong probability by the end of twenty years. Even the patient who is symptom-free when first seen has a 25% chance of deterioration and a 16% chance of death by the end of ten years, and a 60% chance of death after twenty years. The greatest hazards are congestive heart-failure and pulmonary or systemic embolism. The great predominance of women over men with systemic embolism in this series is unexplained.

On this evidence the case for mitral valvotomy for all patients with mitral stenosis might seem overwhelming, but the issue is not quite so clear-cut. The results of purely medical treatment with effective antibiotics and improved methods of treating heart-failure would now probably be considerably better than at the time of the retrospective studies reported here. Moreover, many variables, such as the state of the mitral valve, the degree of incompetence and calcification, and other valve lesions, cannot be assessed in retrospect. Age is also obviously an important factor, and Rowe et al.[4] point out that the survival-time was shorter in older patients. Furthermore, mitral valvotomy is not entirely without risk of morbidity or mortality. Restenosis occurs within five years in approximately 1% of patients per year, often necessitating a further operation[1 2 10 11]; but improved methods of valvotomy by the transventricular route may diminish the incidence.[11 12] Two major hazards to life associated with the operation are systemic embolism due to dislodgement of loose clots from the left atrium, and torrential mitral incompetence which occasionally ensues despite careful attention to technique. There is some

1. Likoff, W., Uricchio, J. F. *J. Amer. med. Ass.* 1958, **166**, 737.
2. Baker, C., Hancock, W. E. *Brit. Heart J.* 1960, **22**, 281.
3. Ellis, L. B., Harken, D. E., Black, H. *Circulation*, 1959, **19**, 803.
4. Rowe, J. C., Bland, E. F., Sprague, H. B., White, P. D. *Ann. intern. Med.* 1960, **52**, 741.
5. Grant, R. T. *Heart*, 1933, **16**, 275.
6. Olesen, K. H. Mitral Stenosis: a follow-up of 351 patients. Copenhagen, 1955.
7. Ellis, L. B., Abelman, W. H., Harken, D. E. *Circulation*, 1957, **15**, 924.
8. Donzelot, E., Heim de Balsac, R., Samuel, P., Beyda, E. *Brit. Heart J.* 1957, **19**, 555.
9. Harken, D. E., Ellis, L. B., Dexter, D., Farrand, R. E., Dickson, J. F. *Circulation*, 1952, **5**, 349.
10. Belcher, J. R. *Brit. Heart J.* 1958, **20**, 76.
11. Wilcken, D. E. L. *Brit. med. J.* 1960, i, 681.
12. Logan A., Turner, R. *Lancet*, 1959, ii, 874.

evidence [13 14] that administration of anticoagulants may diminish the risk of valvotomy in patients with atrial fibrillation, while correction of iatrogenic mitral incompetence by open operation is feasible, though often extremely difficult.

The value of mitral valvotomy in relieving symptoms and prolonging life in patients with critical mitral stenosis causing symptoms or systemic emboli is unquestioned, and no patient who needs the operation should be denied it under these circumstances unless definite contra-indications exist. It is doubtful whether the patient without symptoms or systemic embolism should be subjected to the operation as a prophylactic measure; but Bannister [15] claims that the risk of embolism in cases of moderate stenosis with trivial symptoms is so high that immediate operation should, he suggests, be considered unless the patient is young and still in sinus rhythm. Certainly such patients, and indeed all patients with mitral-valve disease, should be kept under regular medical supervision so that appropriate action may be taken if deterioration sets in.

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

ALTHOUGH the liver is the largest organ in the body, its sheltered position may cause difficulty in assessing its size and shape and deciding whether it is diseased. Clinical examination is the most rewarding and least troublesome method to the examiner conversant with its surface markings.[16] The lower edge is usually palpable in the healthy; and it is felt particularly readily in the emphysematous patient with a low-lying diaphragm. Percussion, which distinguishes its upper border from the lung and the lower border from resonant viscera, is invaluable in detecting a small liver. Occasionally confusion arises in distinguishing a low-lying normal liver from an enlarged diseased liver. Factors contributing to a false impression of hepatomegaly include the subject's occupation and somatotype. The well-developed diaphragmatic movements of a singer or athlete may be responsible for a low-lying, easily palpable liver. In a correlation of the size and slanting angle of the liver with body-type, Fleischner and Sayegh [17] have drawn attention to the easily palpable low-lying normal liver of the ectomorph and the more horizontal high-slung liver of the mesomorph. Antero-posterior and lateral radiographs may help to determine the " slant " of the liver, and screening will convey an accurate impression of the influence of the diaphragm on the position of the liver. In special circumstances, induction of a pneumoperitoneum or gaseous gastric distension may help to distinguish the liver from surrounding structures.

The use of radioactive isotopes to assess liver size, and particularly for the demonstration of filling defects due to hepatic metastases, is still at an experimental stage. Rose-bengal, a dye which was commonly used to assess liver-cell function before bromsulphalein was introduced, is labelled with radioactive iodine; and its distribution in the liver is picked up by an external scintillation counter and recorded on X-ray film.[18 19] Radioactive rose-bengal is rapidly concentrated by liver cells but not by metastases; so space-occupying lesions of the liver can be mapped out as barren non-radioactive areas. Unfortunately, a metastasis must be of considerable size before its presence is obvious by this technique; for, if small, it may be concealed by overlapping normal liver tissue.

Helander et al.[20] in Sweden have attempted to increase the yield of information by using a somewhat similar isotopic technique in conjunction with hepatic venography. Intravenous radioactive gold, which is rapidly taken up by the reticuloendothelial system of the liver, is detected by an automatic scanning scintillation counter; the liver " scintillogram " is altered by the presence of tumour tissue which cannot concentrate the gold. Contrast medium, introduced by hepatic-vein catheterisation, discloses deformities of the hepatic vein and filling defects in the parenchyma of the segment of liver under examination. Helander et al. consider that with further development the scintillographic method will be the simpler and more useful for routine scanning of the whole liver. The radiological technique is preferable for mapping a doubtful area, for it detects small multiple metastases when they are situated close to the veins filled with contrast medium.

Percutaneous [21–23] splenoportography has also been used to detect hepatic metastases. Primary or secondary neoplasm of the liver may produce sufficient distortion of the portal vein and its branches to be seen in a venogram, but similar appearances due to a large regeneration nodule in a cirrhotic liver may be confusing.

These additional techniques for localising anatomical and pathological changes in the liver are still crude and imperfect. With refinement, they may prove of the utmost help in the treatment of hepatic metastases by partial hepatectomy.

MEASLES AND EPILEPSY

THE infectious fevers of childhood are liable to give rise to clinically obvious encephalitis, which may result in death or permanent disability: in some places, indeed, the morbidity and mortality from measles encephalitis has been about the same as that from poliomyelitis. Observations by Gibbs et al.[24] now suggest that encephalitis due to the infectious diseases of childhood is much commoner than clinical observation suggests. Electroencephalograms (E.E.G.) were obtained from 1298 children admitted to hospital with measles, mumps, chickenpox, rubella, or scarlet fever. Of 717 patients with measles 381 (53%) had abnormal E.E.G.s during or immediately after the acute phase of the disease; and of these only 37 had clinical evidence of encephalitis. The E.E.G. changes, which were unrelated to changes in body-temperature, are ascribed by Gibbs et al. to encephalitis. In the great majority of patients these abnormalities subsided, but in about 1% they persisted for months or years. The follow-up study is not yet complete, but already 2 patients have been seen with increasing E.E.G. abnormality culminating in convulsions, and in 1 of these the family doctor diagnosed " idiopathic epilepsy ". Of those who have had an abnormal E.E.G. which subsequently became normal, 3 have shown behaviour disorder or intellectual deteriora-

13. Storm, O., Hansen, A. T. *Circulation*, 1955, **12**, 981.
14. Goodwin, J. F. *in* Pathogenesis and Treatment of Occlusive Arterial Disease (edited by L. MacDonald). London, 1960.
15. Bannister, R. G. *Lancet*, Aug. 13, 1960, p. 329.
16. Sherlock, S. Diseases of the Liver and Biliary System; p. 5. Oxford, 1958.
17. Fleischner, F. G., Sayegh, V. *New Engl. J. Med.* 1958, **259**, 271.
18. Freidell, H. L., MacIntyre, W. J., Rejali, A. M. *Amer. J. Roentgenol.* 1957, **77**, 455.
19. Fee, D. A., Fedoruk, S. O. *New Engl. J. Med.* 1960, **262**, 123.
20. Helander, C. G., Jonsson, L., Larsson, L.-G., Lindbonn, A., Ödman, P. *Acta radiol., Stockh.* 1958, **50**, 533.
21. Leger, L., Proux, C., Arnavielhe, J. *Pr. méd.* 1953, **61**, 1522.
22. Figley, M. M., Fry, W. J., Orebaugh, J. E., Pollard, H. M. *Gastroenterology*, 1955, **28**, 153.
23. Turner, M. D., Sherlock, S., Steiner, R. E. *Amer. J. Med.* 1957, **23**, 846.
24. Gibbs, F. A., Gibbs, E. L., Carpenter, P. R., Spies, H. W. *J. Amer. med. Ass.* 1959, **181**, 1050.

tion—misfortunes which have not been noted in the children whose E.E.G.s were normal throughout.

Of the infectious diseases of childhood measles is the likeliest to cause encephalitis. Instances in both children and adults of encephalitis due to Asian influenza were described in these columns two years ago.[25–28] Since then Olivarius and Fog[29] have reported 12 cases showing neurological complications of Asian influenza, in 5 of which epilepsy developed during the illness or in the ensuing months. It therefore seems possible that, when more is known of the incidence of subclinical encephalitis from all causes, further inroads will be made on the diagnosis of "idiopathic epilepsy" and perhaps of other neurological and psychiatric disorders of uncertain origin.

HÆMORRHAGE FROM THE MIDDLE MENINGEAL ARTERY

No year passes without a few tragic paragraphs in newspapers reporting the death of a child or a sportsman who, between a few hours and a day or so after sustaining an apparently trivial injury to the head, has died of an extradural hæmatoma. At different hospital centres the mortality-rate from this lesion differs widely—from 20% or less to 50% or more.[30] In an article in this issue, Mr. Gibbs insists that the general surgeon should play an important part in these emergencies. He rightly declares that attention should be given to organising the treatment of casualties and emergencies, not simply at isolated points, but over areas. Many of our civilian casualties receive treatment that would not have been tolerated in a forward surgical unit in battle; and some of the defects in this service are made clear by the report of the Nuffield Provincial Hospitals Trust which we reviewed last week.[31]

In general, the measures proposed by Gibbs would certainly help to save lives; but his condemnation of subtemporal decompression is perhaps debatable. Admittedly an extensive clot extending right up to the sagittal line may require an osteoplastic flap to stop continued venous oozing after the arterial bleeding-point has been coagulated; but not all critically ill patients will withstand the operating-time and blood-loss involved in this procedure: the modest aim of preserving or even restoring spontaneous breathing may be the primary goal.

McKissock et al.,[32] reporting an impressively large series of extradural hæmatomas, point out that the lucid interval—that well-known feature of the lesion—was found in only a minority. Of their 125 cases 10 were always conscious, 17 were initially conscious but became unconscious, 35 were initially unconscious and became conscious, and 30 were never conscious; only 33 had a lucid interval. Diagnosis is helped by the finding clinically of ipsilateral dilatation of the pupil and contralateral hemiparesis (and, less often, of papillœdema, dysphasia, and visual-field defects), and radiologically of a fracture with swelling of the overlying subcutaneous tissues; but occasionally all such signs are absent. On the other hand, headache and vomiting—sheet-anchors in the detection of intracranial compression—are almost invariably present. McKissock et al. declare that, if a hæmatoma is suspected but is not found by burrhole exploration, ventriculography or angiography is essential; and, even in their experienced hands, failure to follow this precept has resulted in death.

The work of McKissock and his colleagues on intracranial hæmorrhage [32 33] has shown what may be expected when treatment is undertaken by neurosurgeons prepared in mind, equipment, and administration to treat these emergencies as they arise. How many of our larger hospitals without neurosurgical teams have the resources to deal with such emergencies in the night, except at an exorbitant cost in sleep of a staff that has already worked all day and will work again all next day? And is such an arrangement really satisfactory for the surgery of the coming twenty years? If Gibbs' advice is to be followed, many more hospitals receiving casualties must have surgeons who are prepared to undertake emergency burrholes, and with them should work radiologists prepared to undertake angiography. But though not all may agree with the remedy proposed by Gibbs, he has done well to point to the need for definition of responsibility, and for speedy action, in hospitals which treat or admit these pressing emergencies. "There are," as he says, "still too many deaths from extradural hæmorrhage."

CHILD NEUROLOGY AND CEREBRAL PALSY

A POST-WAR innovation that seems to be working well is the hiring of Oxford and Cambridge colleges for conferences in the vacations. Those who attend these meetings undoubtedly gain much from the subtle effects of the intellectual environment, even if they have to do without some of the amenities of a modern hotel. The second biennial international study group of the National Spastics Society was held at St. Edmund's Hall, Oxford, on Sept. 11–17.

In the two years since the first of these gatherings, the society has greatly extended its research efforts and has become very active in child neurology and developmental medicine, notably by setting up a pædiatric research unit at Guy's, with a professorship endowed by the society. This tendency was reflected at the conference in, for example, the discussion on parietal-lobe function, opened by Dr. W. Ritchie Russell and Dr. E. A. Carmichael, and in the whole morning devoted to the neurological examination of newborn infants. This does not mean that the society is losing interest in "spastics"; but there is a growing feeling that the quickest route to the prevention of cerebral palsy is a roundabout one. The aim is to open up, so far as possible, the whole field of child neurology, in the hope that some useful clues will emerge.

The gathering was truly international and multidisciplinary. But when the society holds its next study group, probably at the same place in 1962, it is likely to include more educationists and to discuss more educational problems—a side of cerebral-palsy research that has hitherto been relatively neglected.

Sir ARTHUR GEMMELL, a past president of the Royal College of Obstetricians and Gynæcologists, died at his home in Liverpool on Sept. 24 at the age of 67.

Dr. A. M. KENNEDY, emeritus professor of medicine in the University of Wales, died in Cardiff on Sept. 24.

25. Flewett, T. H., Hoult, J. G. *Lancet*, 1958, ii, 11.
26. McConkey, B., Daws, R. A. *ibid.* p. 15.
27. Bental, E. *ibid.* p. 18.
28. *ibid.* p. 32.
29. Olivarius, B. de F., Fog, M. *Danish med. Bull.* 1959, **6**, 248.
30. See *Lancet*, 1959, ii, 604.
31. Casualty Services and their Setting. London, 1960. See *Lancet*, Sept. 24, 1960, pp. 689, 698.
32. McKissock, W., Taylor, J. C., Bloom, W. H., Till, K. *ibid.* July 23, 1960, p. 167.
33. McKissock, W., Richardson, A., Walsh, L. *ibid.* 1959, ii, 683. McKissock, W., Richardson, A., Walsh, L. *ibid.* 1960, i, 1203. McKissock, W., Richardson, A., Bloom, W. H. *ibid.* p. 1365.

Special Articles

EXPERIENCE OF A NEONATAL SURGICAL UNIT

THE FIRST SIX YEARS

ISABELLA FORSHALL
M.B. Lond., F.R.C.S.

P. P. RICKHAM
M.S. Lond., F.R.C.S., D.C.H.

CONSULTANT PÆDIATRIC SURGEONS,
ALDER HEY CHILDREN'S HOSPITAL, LIVERPOOL

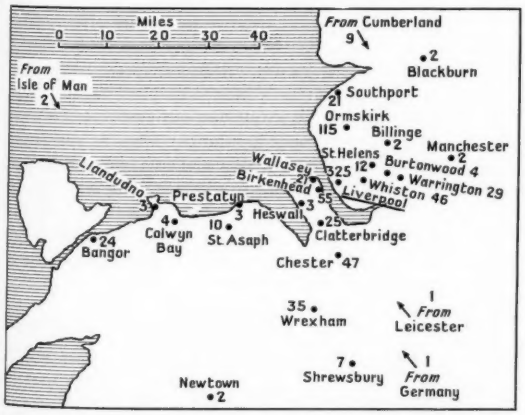
A SURVEY carried out some years ago (Rickham 1952) showed that, in 1949, 75 infants with urgent surgical conditions were born in the area covered by the Liverpool Regional Hospital Board. Roughly a third (21) of these infants failed to reach a hospital, and all of these died. The remainder (54) were operated on in fourteen different hospitals, and of these 33 (66%) died. This unsatisfactory state of affairs suggested that an attempt should be made to organise a neonatal surgical service. After considerable preliminary work a small neonatal surgical unit was opened at Alder Hey Children's Hospital, Liverpool, on May 1, 1953. The layout and equipment of this unit have been previously described (Rickham and Mason 1953). It contained 8 cots, 2–6 incubators, and rooms for 2 nursing mothers.

Patients Treated

We survey here the work done in the unit during its first six years. 813 infants were admitted, and of these 196 (24%) died. Pædiatricians, obstetricians, and general practitioners have been encouraged to send infants to the unit if there is only a suspicion that an urgent surgical condition may be present, so it is not surprising that some infants on admission are found not to require operation, but to have a medical condition. 663 infants admitted to the unit underwent operation; there were 177 deaths (26·7%) in this group.

Area of Drainage

Nearly every infant under 4 weeks of age with an urgent surgical condition in the area of the Liverpool Regional Hospital Board and North Wales is now sent to the unit; relatively few infants came from other regions (see map).



Sketch map of Liverpool region, North Wales, and South Lancashire showing places from which newborn infants with urgent congenital conditions were sent to the neonatal surgical unit, and numbers sent between May, 1953, and May, 1959.

The majority of cases came from maternity units (75% of babies in the Liverpool region are born in hospital); only a small proportion of the infants admitted had been born at home. As will be seen from the map, the area covered by the neonatal surgical service is relatively compact.

There is close collaboration between pædiatricians in the area and the pædiatric surgeons running the unit, so that it has been possible to standardise methods of diagnosis and arrangements by which babies are transported and admitted. The pædiatricians working in maternity units have become " operation-conscious ", and there is little doubt that the improved results following neonatal surgery in the period under survey are partly due to early diagnosis and prompt transfer.

Lectures, clinical demonstrations, refresher courses for doctors, and regular lectures for midwives working in the region have encouraged awareness of surgical conditions in newborn babies and early admission of suspicious cases.

Staff

Until lately two pædiatric surgeons work in the unit aided by two surgical registrars and two house-surgeons, so that one team was always available.* One of two pædiatric anæsthetists supervises all anæsthetics given to neonates. An anæsthetic registrar is on call day and night; this is of great importance for the prompt treatment of respiratory distress in the preoperative and postoperative periods.

It has been found that a departmental sister-in-charge, four sisters, and a varying number of nurses in training is the minimum nursing establishment required during the day. Two sisters helped by nurses in training are necessary for night duty. This large number of trained nursing staff is essential, as only those with considerable experience and special training can look after these infants satisfactorily. Devoted expert nursing is an essential factor in successful treatment; whenever the number of trained nurses has dropped below the required minimum, the standard of supervision and of nursing technique has fallen.

Diagnosis

In malformations of the alimentary tract causing obstruction in the first few days of life, the clinical picture will usually suggest an urgent surgical lesion, and the exact diagnosis can nearly always be made by radiography (Rickham 1959a). On the whole we prefer that the radiological examination be made after the child has been admitted to the unit, but for cases examined in other hospitals a standard radiographic technique is used.

In suspected intestinal obstruction a single anteroposterior film with the infant in the erect position, without contrast medium, is taken. This will usually show the situation and nature of the lesion (fluid levels, free gas under the diaphragm, intra-abdominal calcification, &c.), and will also reveal intrathoracic malformations (diaphragmatic hernia, mediastinal cysts, lung cysts, &c.), as well as pulmonary collapse, pneumonia, and cardiac enlargement or displacement.

Special radiological examinations are required for some conditions, such as œsophageal atresia, Hirschsprung's disease, and urinary obstruction, but the importance of limiting exposure of infants to radiation is constantly kept in mind. A special screen for the radiological examination of infants which minimises radiation of the attendant is used in the unit (Rickham 1959b).

* Since the appointment of Mr. H. J. Johnston the teams have been increased to three.

Transport

It has been shown that the transportation of these infants over considerable distances does little harm (Forshall and Rickham 1953) provided an experienced nurse accompanies the infant. The baby is usually transported lying flat on his side in a carry-cot; warmth is supplied by hot-water bottles. In all cases of intestinal obstruction or suspected obstruction a no. 3–4 soft rubber catheter is passed through a nostril into the stomach; the nurse aspirates the stomach every ten minutes. Should the infant none the less aspirate mucus or vomitus, the nurse sucks out the pharynx by means of a mucous extractor (Rickham 1957a). An oxygen cylinder and an apparatus for humidifying oxygen are at hand in the ambulance. The greatest care should be taken to prevent the body-temperature falling during transport, especially in premature infants.

Admission

Babies from maternity departments are admitted directly to the main ward of the unit. Infants born at home or admitted via a general pædiatric unit, and any baby in whom there is the slightest suspicion of contact with infection, are nursed in isolation cubicles for several days before being transferred to the main ward. Despite great care, cross-infection occasionally occurs—nearly always a specific *Escherichia coli* infection.

Preoperative Treatment

On admission, infants needing operation are placed in special surgical incubators at a temperature of 85°F, in an atmosphere of 100% humidity. Minor surgical, radiological, and anæsthetic procedures as well as balance tests can be carried out in the incubators without much disturbance of the children (Rickham and Jenkins 1960). The body-temperature is recorded by an electric thermometer; frequent readings can be made without moving the infants. Investigation and, as far as possible, treatment of babies with subnormal temperature are deferred until the body-temperature has risen to normal. Preoperatively penicillin, streptomycin, and vitamin K (1 mg.) are injected transmuscularly. In the cases in which investigation of the blood chemistry is essential, 0·1 ml. of blood is obtained by heel stab (Rickham 1957b). All infants have a cut-down infusion before operation; only a minority require correction of dehydration and electrolyte imbalance preoperatively.

In cases of intestinal obstruction, constant gastric suction at a negative pressure of 20 cm. of water via a catheter passed through the nose is instituted. Continuous gastric suction, will often completely deflate a distended abdomen in a newborn infant, as well as preventing aspiration of vomitus.

Postoperative Treatment

The infants are transported back from the theatre to the unit in their incubators, and they are nursed in incubators during the immediate postoperative period. Many of these neonates, and especially those operated on for obstruction of the alimentary tract, need protracted low-pressure gastric suction and intravenous therapy, under accurate biochemical control (Rickham 1957c). Conscientious, skilled nursing and continuous supervision by the surgeon are essential in the immediate postoperative period. The commonest cause of sudden death during this period is inhalation of vomitus or mucus; a trolley carrying all the necessary equipment to deal with this emergency is always ready in the ward.

Operation and Anæsthesia

The importance of correct replacement of blood-loss (Rickham 1954a, 1959c) cannot be overemphasised. The great advances in neonatal anæsthesia, the routine use of endotracheal anæsthesia with controlled respiration, using oxygen, nitrous oxide, and suxamethonium chloride (Rees 1958) have made protracted operations on neonates relatively safe. As no ether or cyclopropane is used, diathermy can be employed; and this considerably reduces blood-loss and operation-time.

Prematurity

The cases admitted to the unit differ from cases in previously published series, in that practically every infant with a surgical abnormality born in the area of drainage is included. This explains the high incidence of very premature infants and of infants with multiple, severe, malformations. We have only very occasionally saved an infant who, in addition to a malformation amenable to surgery, has a malformation of one or several other systems (e.g., cardiac or cerebral). It seems likely that in these children the prognosis will always be poor. It should, however, at least theoretically, be possible to save more premature infants with a single abnormality. Our operative mortality in premature infants is still very high. 222 (35%) of the 663 infants operated on in the past six years were premature (under $5^1/_2$ lb. in weight). While the operative mortality of the 441 full-term infants was 12·4%, that of the 222 premature infants was 50·4%, and in the 87 infants weighing under $4^1/_2$ lb., the operative mortality rose to 60·9%.

This high mortality in premature babies is partly due to the high incidence of multiple abnormalities in these infants—in our series 32·9%, as opposed to 10·9% in full-term infants. There is great difficulty in nursing these infants through the postoperative period (Rickham 1957d). The swallowing and coughing reflexes are incompletely developed, and aspiration of mucus and vomitus is common. The immature state of the lungs predisposes to pulmonary complications, and the incidence of sclerema is higher in premature infants. Satisfactory results have occasionally been achieved, our smallest surviving infant with œsophageal atresia weighed 2 lb. 8 oz., with pyloric stenosis 2 lb., and with ileal atresia 3 lb.

Conditions Treated

The surgical conditions treated in the unit have been grouped under fifteen headings (see accompanying table).† The cases are further subdivided into four categories: (1) full-term infants with a single major malformation; (2) full-term infants with multiple malformations, each of which occurring alone would endanger life; (3) premature infants with one major malformation; (4) premature infants with multiple malformations. The table shows that the operative mortality for full-term infants with one major malformation is relatively low. The operative mortality in any series will depend on the distribution of infants between the four groups.

Malformations of Central Nervous System

The most common type of case admitted is severe spina bifida with or without hydrocephalus. Formerly these cases seldom came to surgery before they were 4 weeks of age (Rickham 1957e). Recent advances in the treatment of myelomeningocele, and especially the introduction of the Spitz-Holter valve for the drainage of hydrocephalus (Spitz 1959), have resulted in the

† To avoid confusion cases with multiple malformations are shown only once—i.e., under the main malformation.

NUMBERS OF CASES IN MAIN GROUPS OF DISORDERS OPERATED ON IN THE NEONATAL SURGICAL UNIT BETWEEN MAY, 1953, AND MAY, 1959

Condition	Total no.	Total deaths	Full-term infants with one malformation*	Full-term infants with multiple malformations*	Premature infants with one malformation*	Premature infants with multiple malformations*
Malformations of central nervous system	85	*13*	72 (*10*)	3 (*0*)	9 (*2*)	1 (*1*)
Malformations of upper respiratory tract	14	*2*	10 (*0*)	1 (*1*)	3 (*1*)	0
Œsophageal atresia	83	*43*	26 (*4*)	11 (*6*)	20 (*9*)	26 (*24*)
Pyloric stenosis (premature infants only)	37	*4*	..	..	33 (*1*)	4 (*3*)
Intrinsic intestinal obstruction	57	*13*	26 (*1*)	7 (*1*)	14 (*3*)	10 (*8*)
Extrinsic intestinal obstruction	55	*2*	36 (*0*)	1 (*0*)	13 (*0*)	5 (*2*)
Peritonitis	41	*15*	25 (*4*)	1 (*1*)	14 (*9*)	1 (*1*)
Meconium ileus	23	*19*	9 (*6*)	2 (*2*)	9 (*8*)	3 (*3*)
Hirschsprung's disease	28	*5*	23 (*4*)	0	5 (*1*)	0
Anal and rectal atresia	65	*12*	35 (*0*)	12 (*5*)	11 (*2*)	7 (*5*)
Exomphalos	57	*23*	31 (*5*)	8 (*4*)	11 (*9*)	7 (*5*)
Malformations of genitourinary system	38	*9*	27 (*3*)	3 (*2*)	5 (*1*)	3 (*3*)
Diaphragmatic hernia	18	*7*	10 (*1*)	0	7 (*5*)	1 (*1*)
Obstructive jaundice	8	*1*	7 (*0*)	0	1 (*1*)	0
Tumours	20	*3*	17 (*2*)	0	3 (*1*)	0

* No. of deaths in italics.
In cases with multiple malformations the case is shown only once—i.e., under the main malformation.

admission of more and more newborn infants. Myelomeningoceles and myeloceles are now operated upon as soon as possible after birth, before the covering membranes become infected. In more than half of the cases, hydrocephalus rapidly develops postoperatively. Insertion of the Spitz-Holter valve in patients of this age is associated with some special difficulties, but on the whole the results have been encouraging. There is little doubt that there will be a further increase in the number of cases with these malformations admitted to the unit.

Obstruction of Upper Respiratory Tract

Apart from rare instances of laryngeal or subglottic stenosis necessitating urgent tracheotomy, such cases are of two main types. The first is severe micrognathia, usually associated with cleft palate (Pierre Robin syndrome), in which there may be severe respiratory difficulty in addition to difficulty in feeding. Skilled nursing with the infant in the semiprone position and feeding by gavage will usually overcome these difficulties, but occasionally tracheotomy is required and in 1 case gastrostomy had to be performed. The second type is bilateral posterior choanal atresia, treatment of which consists in perforating the bony or cartilagenous septa occluding the posterior nares, thus establishing a nasal airway. In both types of case, postoperative treatment is lengthy and difficult and taxes the nursing staff to the utmost.

Œsophageal Atresia

It will be noticed from the table that the operative mortality in full-term infants with œsophageal atresia, without other malformations, is small. Unfortunately the number of premature infants, and especially the number of premature infants with multiple malformations, in this series is very high (Forshall 1957a), and the mortality in these groups is enormous. The commonest associated malformations are severe cardiac lesions, incompatible with survival for more than a few days, and rectal and duodenal atresia. Duodenal atresia carries a very bad prognosis. Today leaks in œsophageal anastomoses are not necessarily fatal, but necessitate prolonged and often difficult postoperative management. Nursing these children in incubators in an atmosphere of 100% humidity, restriction of intravenous fluids, and avoidance of unnecessary handling are the main factors which help to lower the mortality.

Pyloric Stenosis

Most infants with pyloric stenosis are admitted to, and treated in, the general pædiatric surgical wards; only premature infants are admitted to the unit. Of the 33 cases, nearly a third weighed less than $3^1/_2$ lb. Of the 4 deaths 1 was due to intracranial birth trauma. 2 infants had a blood dyscrasia of prematurity; both weighed less than 3 lb., and, in both, severe bleeding into the lungs and intestinal and urinary tracts started shortly after operation.

Intrinsic Intestinal Obstruction

In roughly half the cases, the obstruction was in the duodenum (Forshall 1947), and in the other half it was in the jejunum or ileum; in only 2 cases was the obstruction in the colon. Most of the cases in this group had atresia; in roughly a quarter of the cases there was a high-grade stenosis. About a third of the duodenal obstructions were associated with annular pancreas (Rickham 1954b). In full-term infants without other gross malformations survival-rate was high.

Extrinsic Intestinal Obstruction

These were mostly cases of anomalous rotation of the midgut with volvulus or of obstruction due to intraperitoneal bands; a few had strangulated herniæ. In only 1 of these cases was it necessary to open the intestinal lumen, which explains the low operative mortality. 1 death occurred in a premature infant and was due to kernicterus.

Peritonitis

Under this heading, two different conditions are included: sterile meconium peritonitis due to intrauterine extrusion of meconium from the bowel into the peritoneal cavity (Forshall et al. 1952), and bacterial peritonitis (Rickham 1955, 1959d). Many of the infants had intestinal atresia, perforation, or gangrenous gut. The mortality was high.

Meconium Ileus

This is still the most fatal condition encountered in neonatal surgery. Most children now survive the operation to relieve intestinal obstruction, but die of fulminating bronchopneumonia in the first few postoperative days or weeks. Of 23 cases only 10 left the unit alive, and all but 4 died in the first year of life.

Hirschsprung's Disease

Practically all cases of Hirschsprung's disease are now seen as neonates presenting with symptoms of intestinal obstruction. In most cases the obstruction can be relieved by enemas or by passing a flatus tube, only to recur after a few days or weeks. Several of our earlier cases died of fulminating staphylococcal enteritis or aspiration of vomitus. Since a colostomy has been instituted as soon as the diagnosis is made, the mortality has fallen. Rectosigmoidectomy is performed when the infant is over 15 lb. in weight.

Anal and Rectal Atresia

The operations for anal abnormalities are relatively minor, and there is a very low operative mortality. An abdominoperineal pull-through operation is used for rectal atresia; this is a severe operation, but the mortality is not excessive. Most deaths in this group occurred in babies with associated malformations. Œsophageal atresia and malformations of the cardiovascular and urogenital system are especially common; cardiac lesions are not infrequently of such severity as to be at present incompatible with life (Forshall 1957b).

Exomphalos

The results in this group are strikingly poor. Exomphalos minor is not associated with any operative mortality. Exomphalos major not only is a dangerous condition per se, but

is commonly associated with other serious malformations. Further, many of the cases in this series were grossly premature. This explains the fact that, while only 1 in 8 full-term infants with exomphalos died, the total mortality was nearly 50%.

Malformations of Genitourinary System

This group includes a wide variety of lesions—mainly obstructions of the urinary tract causing renal failure shortly after birth. Most of the infants survived operation, but in many renal damage was so severe that the long-term prognosis is poor.

The number of cases of gross malformations of the urinary tract operated on in the unit is increasing each year. The operative treatment of ectopia vesicæ (closure of the ectopic bladder and splayed-out pelvic ring) in the immediate postnatal period will augment the number of cases admitted in the future.

Diaphragmatic Hernia

The number of infants with this malformation is relatively small. The mortality is again high because of the high incidence of associated deformities incompatible with life—especially cardiac and pulmonary malformations.

Obstructive Jaundice

Only a few of the children with obstructive jaundice will come to surgery during the neonatal period. Usually these infants are more than 4 weeks old before gradually increasing jaundice results in their reference to a pædiatric surgeon. This explains the relatively small number admitted to the unit. Exploration, liver biopsy, and, if possible, an operative cholecystogram should be carried out in cases in which a mechanical obstruction cannot be excluded by laboratory tests. In only about 10% of these cases will a mechanical block of the extrahepatic bile passages be found and operative correction become a possibility (Hall 1957).

Tumours

Sacrococcygeal teratoma is the commonest of tumours in newborn infants. Most of these tumours are benign, but occasionally malignant tissue is found in a teratoma removed immediately after birth. Early excision is, therefore imperative. A wide variety of benign and malignant tumours was encountered; individually rare, the total is not inconsiderable.

Follow-up of cases

All infants discharged from the unit are followed up as outpatients. Monthly outpatient clinics are held in certain centres outside Liverpool to save the mothers travelling too great distances. In the city of Liverpool the care of premature infants, after discharge, is greatly aided by the premature domiciliary nursing service provided by the medical officer of health.

Developments

The unit was started with the absolute minimum of financial aid. Equipment was very limited, and, because of the rapidly increasing numbers of admissions, space soon became inadequate. In addition, there were inadequate arrangements for nursing the many premature infants admitted, and the accommodation for nursing mothers was unsatisfactory.

The experience gained in six years has enabled us to formulate various improvements, and, with the generous help of the regional board and the hospital management committee, the unit has now been reorganised. The main improvements are: the provision of 2 more isolation cots; the building of an air-conditioned " hot room " with a constant temperature of 85°F, and a humidity of 90%, large enough to hold 6 incubators for premature infants; and the addition of a small ward for convalescent infants, holding 4 cots. Infants nursed in the hot room can be taken out of the incubators without lowering their environmental temperature and humidity, thus facilitating nursing and minor operative procedures. There are now 12 cots, 6 incubators, and rooms for 2 nursing mothers in the reorganised unit. In addition, there have been a number of structural improvements, the most important being a sister's room with glass walls allowing simultaneous supervision of the two wards and the " hot room ".

Conclusions

There is little doubt that the Liverpool unit for the surgical treatment of newborn infants has proved its value. It is of course possible to achieve good results nursing such infants in general wards or side-wards, but the work is much facilitated by concentrating cases in one unit. Even more important, the unit provides ideal conditions for the training of medical and nursing staff, and adequate material for postgraduate teaching.

The Liverpool region lent itself to this experiment because the area is small but thickly populated. The inclusion of North Wales has shown that distance is no bar to the establishment of an efficient neonatal surgical service. Such a centre is best situated within a large children's hospital attached to a university, thus insuring the cooperation of pædiatricians, pædiatric anæsthetists, pathologists, biochemists, radiologists, and the various research-workers necessary for the development of this still young branch of surgery. Most of the provincial university centres in the country have the requisite staff and conditions for the establishment of such a unit.

REFERENCES

Forshall, I. (1947) *Brit. J. Surg.* **35**, 58.
— (1957a) *Brit. J. Clin. Practice*, **11**, 824.
— (1957b) *ibid.* p. 842.
— Rickham, P. P. (1953) *Brit. med. J.* i, 782.
— — Hall, E. G. (1952) *Brit. J. Surg.* **40**, 31.
Hall, E. G. (1957) *Brit. J. clin. Practice*, **11**, 859.
Rees, G. H. (1958) *Brit. med. Bull.* **14**, 38.
Rickham, P. P. (1952) *Lancet*, i, 332.
— (1954a) *Arch. Dis. Childh.* **29**, 304.
— (1954b) *ibid.* p. 80.
— (1955) *ibid.* **30**, 23.
— (1957a) *Brit. J. clin. Practice*, **11**, 816.
— (1957b) The Metabolic Response to Neonatal Surgery. Cambridge, Mass.
— (1957c) *Brit. J. clin. Practice*, **11**, 833.
— (1957d) *Arch. Dis. Childh.* **32**, 508.
— (1957e) *Brit. J. clin. Practice*, **11**, 847.
— (1959a) *Pediat. Clin. N. Amer.* **6**, 955.
— (1959b) *Brit. med. J.* i, 716.
— (1959c) *Lancet*, i, 556.
— (1959d) *Dtsch. Z. Chir.* **292**, 427.
— Jenkins, J. M. (1960) *Arch. Dis. Childh.* (in the press).
— Mason, H. R. (1953) *Hospital, Lond.* **49**, 605.
Spitz, E. B. (1959) *Pediat. Clin. N. Amer.* **6**, 1215.

THE INDUSTRIAL THERAPY ORGANISATION (BRISTOL)

A DEVELOPMENT OF WORK IN HOSPITAL

DONAL F. EARLY
L.R.C.P.I., D.P.H., D.P.M.
CONSULTANT PSYCHIATRIST, FISHPONDS HOSPITAL, BRISTOL

INDUSTRIAL work in hospital has been reviewed by Charlton (1959), who found that 58 hospitals in this country were carrying out industrial therapy.

At Fishponds Hospital, which has altogether about 1200 patients, the capacity of our scattered factory rooms was increased from 14 patients in January, 1958, to 385 patients in December, 1959. The work is mainly manufacture of ball-point pens, box-making, stamp preparation, and telephone dismantling. The department functions under joint nursing and industrial supervision; at present there are 6 industrial and 8 nursing staff (3 unqualified women, 3 unqualified men, and 2 qualified men).

The patients work 25 hours a week, singly or in teams or groups, and are paid " the rate for the job ". Total

earnings by patients in November, 1959, amounted to more than £1300. The hospital management committee deduct 10%; but, as Stanley (1959) points out, this does not benefit the hospital nor the patients who earn the money. This disagreeable anomaly should be rectified.

To occupy consistently a third of the patients in a chronic hospital is obviously a desirable aim, but it is not an end in itself. Patients tend to settle down as they have been encouraged to in the past, with a slightly better standard of living, and an "industrial aristocracy" tends to replace the old privileged maintenance-department worker. The ultimate aim of discharge may be lost sight of by patients and by staff.

The standard of work maintained by patients in the hospital industrial therapy department has been consistently high, and the industrialists have been impressed by the quality of their work. It was difficult initially to overcome the inertia which beset the people whom we wished to interest; but with the help of a director of one of our firms, a considerable number of industrialists were persuaded to visit the hospital and see the patients at work. They were impressed by the commercial possibilities and by the philanthropic aspect of the work, and felt that further employment-training is necessary if patients are to be re-employed in open industry. With this aim in view Industrial Therapy Organisation (Bristol) Limited was formed.

I.T.O. (Bristol) Ltd., is a non-profit-making company limited by guarantee and having registered offices in York Street, St. Phillips Marsh, Bristol. It has been formed to administer a scheme designed to offer medically and industrially supervised employment training under conditions approximating as nearly as possible to ordinary factory conditions, as a second stage toward complete industrial rehabilitation. In the third stage of rehabilitation, worker-patients who improve under these conditions will be taken by sympathetic employers for a further period of training under "open" factory conditions and will subsequently, if successful, be employed if possible or be recommended by the employer.

The chairman of the company is chairman of the Engineering and Allied Employers' West of England Association.

The Churches are represented by the Bishop of Bristol, the Bishop of Clifton, the president of the Bristol Free Church Federal Council, and the industrial adviser to the Bishop of Bristol. Civic interests are represented by the Lord Mayor of Bristol, two justices of the peace (one of whom is the chairman of the Fishponds H.M.C.), the chairman of the health committee and the chairman of the mental-health subcommittee of the local authority, and the medical officer of health. The chairman of the South-Western Regional Hospital Board has agreed to serve together with an industrial medical officer, a consultant psychiatrist, and a general practitioner. Industry is represented by the directors of 9 leading firms in the city, the chairman of I.T.O. and his deputy, the regional controller of the Ministry of Labour, and the regional industrial adviser of the B.B.C. The regional secretary and the local secretary of the Transport and General Workers Union and the president of the Bristol Trades Council, and our public-relations officer also serve on the board. Local firms of solicitors and of accountants supply us with their advice.

There was an initial storm in a teacup before the formation of I.T.O. was proposed. An ill-informed statement at the Bristol Trades Council gave rise to such headlines in the local press as "Mentally Ill in Danger" (*Western Daily Press*, Oct. 10, 1959), and the word "exploitation" was used in reference to the work of patients in hospitals. When, however, trade-union representatives visited the department and inquired into its aims and operation, the Bristol Trades Council were assured by their president that there was no exploitation and that the work was of practical therapeutic benefit (*Bristol Evening Post*, Jan. 22, 1960). Thereafter, the unions have not opposed industrial therapy in hospital nor the formation of I.T.O., but have been strong in support—in the case of the Transport and General Workers Union, strong in financial support. Mr. Frank Cousins, general secretary of the Transport and General Workers Union, when he visited the factory, described I.T.O. as "a wonderful experiment" and as a "worth-while project" and added: "We are proud that we have been able to do something to help I.T.O." (*Western Daily Press* March 26, 1960).

Premises

I.T.O. has leased a disused school in York Street, St. Phillips Marsh.

This building was in very poor repair but was renovated by one of the participating firms. It contains about 7250 sq. ft. of floor space. Daylight lighting is good, but all electric wiring and fitments have had to be renewed. Heating is by means of a rather antiquated coal-burning furnace with hot-water circulation; in the summer this will be converted to oil. Sanitary facilities are adequate, but much work had to be done on the water and drainage systems. The roof also needed much attention, most of the lead having been removed. Apart from factory space, we have a fair-sized canteen reasonably furnished, a general administrative office, a rest-room, and a medical office.

Finances

It is not proposed to establish I.T.O. as a Remploy-type factory nor as a sheltered workshop, but rather as a training factory, stimulating initiative. We hope that, as such, it will be self-supporting. The money necessary to start has been contributed by various people—mainly by industry, with substantial sums from the Bishop of Clifton and from the Transport and General Workers Union. The industrialists placing work with I.T.O. pay the full labour costs of the job and have agreed to add $33\frac{1}{3}\%$ on cost to this price; this will cover the factory overheads. The success of the worker-patients will thus be the only source of income of I.T.O.

The main sources of expenses have been estimated as follows:

Staff.—Exclusive of medical and nursing supervision, it is estimated that 150–200 operatives would require a full-time staff of 8: a secretary (salary £750); a works manager (salary £1000); general supervision, approximately 5 (£2500); general labourer (£500); total £4750.

Other expenses.—Rent, £450 per annum; heat, light, and repairs, £1500; telephone, £100; general supplies, cleaning material, &c., and stationery, approximately £500.

It was thus envisaged that the Organisation could be run for a total outlay of £7500 per annum.

With an on-cost charge of $33\frac{1}{3}\%$ on work invoiced, it is estimated that the Organisation would require a turnover of approximately £28,000 per annum to be self-supporting. If the average pay were £5 a week, 120 operatives would be required to achieve this turnover; and this is probably attainable.

Medical and Nursing Supervision

The hospital management committee of the Fishponds Hospital agreed to allow nursing supervision for hospital patients; and we have started with a nursing supervisor, a ward sister, a charge nurse, and 2 unqualified staff, 1 of

whom is a student male nurse. Medical supervision is provided by the doctors who are in charge of the patients, but it is hoped that in the future some more definite arrangement may be possible. The medical officer of health has seconded a health visitor, who at present is working half-time and whose prime duty will be to act as social worker. As additional patients come from the community, more social workers will be seconded by the medical officer of health. When other hospitals send patients they will be expected to provide nursing supervision for them. We have arranged for a weekly staff meeting of nursing, social, industrial, and medical workers.

Choice of Patients

To start the I.T.O. factory on March 7, 1960, 20 patients were chosen from among those who had a good record in the industrial therapy department of Fishponds Hospital. They were chosen by consultation with doctors and nurses, nursing supervisors, and industrial supervisors. Regard was paid to industrial ability, stability, and sociability. These 20 patients were joined at work by 5 who had been attending Fishponds Hospital as day patients from their own homes. We began with the assembly of ball-point pens for Messrs. Tallon Ltd. Subsequently some box-making and stapling and gluing machinery were installed by Messrs. E. S. & A. Robinson, and a further 30 patients started from the hospital. At present 61 patients (21 male and 40 female) attend daily from Fishponds Hospital and 18 day patients (12 male and 6 female) from their own homes.

We anticipate that the complement of the factory at full capacity will be 120–150. After the " teething troubles " have been overcome, the factory will offer facilities to other patients in the Bristol clinical area according to the following procedure:

I.T.O. will accept applications for places in the factory from all consultant psychiatrists in the Bristol clinical area and from doctors in charge of day hospitals and occupational therapy departments, and from the medical officer of health. No applications will be accepted from patients directly. In the event of more than one application for a vacancy, the selection will be made by the medical directors of I.T.O. Applicants will be accepted for a month's initial practical trial, following which the industrial, nursing, and medical staff will review each patient's suitability for further training. During this assessment period earnings will be limited to £2, to obviate difficulties with National Insurance. If the patient proves suitable, training will be continued; if unsuitable, the decision will be discussed with the doctor who referred the patient. No subnormal patients will be accepted until the needs of chronic psychotics have been assessed.

Since I.T.O. is not a remploy factory nor a sheltered workshop, there must be movement of patients through the factory if it is to fulfil its purpose. Its capacity is unlikely to exceed 150 places, so the time that any patient may remain must be curtailed. No limit has been stated; but, when it is apparent on the basis of psychiatric, industrial, and nursing reports that the patient is no longer making progress and is unlikely to proceed further in industrial training, he must then be discharged from I.T.O. Possibly at this stage patients will be acceptable in Remploy factories or in sheltered workshops. The Ministry of Health is certainly more aware of the needs of the chronic psychiatric invalid than in the past; and it has emphasised the need to prevent chronicity in mental-hospital patients (Ministry of Health 1959). I.T.O. is now considering the possibility of providing work for patients on a more permanent basis.

Terms of Employment

Hours of Work

The patients work from 8.15 A.M. to 5.15 P.M. five days a week with one hour's lunch-break and two quarter hour tea-breaks. As part of the training routine patients " clock in " and " clock out " as in an ordinary factory.

Transport

22 patients travel by hospital bus for which no charge is made, and 36 by a bus chartered by I.T.O. at preferential rates. As the patients ride in each bus alternately, the overall cost per patient will be 3*s*. 4*d*. per week. Outpatients make their own travel arrangements.

Food

To provide in the factory a canteen which could supply a cooked meal at midday has been impossible owing to the initial outlay and the consequent high cost to the patient of meals. Patients therefore bring a packed lunch, and hospital patients have a cooked meal when they return in the evening.

Patients' Finances

I.T.O. does not aim to pay big wages, but rather to provide further training under factory conditions. The amount earned will largely depend on the type of work available in the factory. Wages must be greater for a forty-hour-week than they have been for a twenty-five-hour week in hospital; otherwise the main incentive will be lost.

There are three main administrative departments whose regulations act as a financial deterrent to patients in the initial stages of industrial rehabilitation—the Ministry of Health, the Ministry of Pensions and National Insurance, and the National Assistance Board.

The *Ministry of Health's* (1958) memorandum on the recovery of part costs from patients going out to remunerative work was designed to cover circumstances very different from those created by I.T.O.—namely, those of a patient who goes out to work full-time from hospital and who earns normal full-time wages of £6–£10 per week. In the case of patients earning £2–£5 a week the terms of the memorandum stifle initiative; for example, working full-time at I.T.O., a single man with no dependants and no sickness allowance must earn £4 a week gross to have £1 13*s*. 4*d*. net. In hospital, working a twenty-five-hour week, he can earn up to £2 a week without complication, so by doubling his effort and working an additional fifteen hours a week he will sustain a loss of 6*s*. 8*d*. To mitigate this position the Ministry has agreed that " the formula in H.M. (58) 72 may be modified by allocating £2 15*s*. to the patient, instead of £1".

The regulations of the *Ministry of Pensions and National Insurance* are an even greater danger, especially for the patient whose wife and family are in benefit. Earning over £2 a week entails the cessation of National Insurance benefits for a wife and children, and the patient becomes liable to National Insurance contributions. Since the earnings in I.T.O. are unlikely to exceed £4–£5 per week (less in the initial stages), a class-2 (self-employed) National Insurance contribution represents a very high proportion of earnings, the disproportion is greater the lower the earning group, the contribution being 30% of £2 or 15% of £4 per week. Not surprisingly, therefore, patients " hold back " and are virtually prohibited by regulations from exercising their initiative, which might lead to discharge and to their ceasing to be a charge on State funds.

National Assistance Board.—The Ministry of Health informed us that the N.A.B. would be able to meet the essential needs of the patients' dependants when the National Insurance allowance ceases, and that the N.A.B. would in many cases compensate for the loss of dependants' part of sickness benefit. Local officials of the Ministry of Pensions and National Insurance and of the N.A.B. have been most helpful, but lack of resilience in their regulations render individual cases of hardship inevitable when patients exceed a low limit of earning.

Furthermore, a patient who qualifies to pay a board-and-lodging charge to hospital and who has dependants drawing National Assistance may find that the Ministry of Health and the National Assistance Board are each claiming from his earnings—for board-and-lodging and for dependants' allowance respectively.

The report of the National Insurance Advisory Committee on the Question of Long-term Hospital Patients (1960) declared that there must be a point where a patient's earnings become inconsistent with his receiving National Insurance benefit, and the committee concluded that there was no evidence at the present time that the earnings limit of 40*s.* a week was acting as a disincentive. In I.T.O. we have no doubt that the £2 limit acts as an obstacle in the initial stages of work outside hospital when earnings are low and depend on the patient's efforts. The committee considered that the limit "should remain at 40 shillings per week for the present". It obviously foresaw that changes would be necessary, and I consider that in the present circumstances further consideration is essential.

Unlike short-term illness, long-stay patients are not unfit for work today and fit for full-time employment tomorrow. It will require time to re-establish the habit of normal work, and in most cases failure will result. We wish to teach patients to assume normal responsibilities—to pay their National Insurance contributions, to pay income-tax if due, to pay for all or part of their keep, their transport costs, and their meals at work—but this must await the third stage of rehabilitation when the patient draws a full economic wage. If the Ministry of Health (1958) and the National Insurance Advisory Committee believe in the therapeutic value of work, as they say they do, then together with the N.A.B. some scheme must be devised which will encourage patients to work.

Social Resettlement

The Medical Research Council (1959), discussing the conditions of resettlement of schizophrenics, says:

"It appeared likely that a proportion of these patients could be restored to life in the community provided that their social behaviour was such as to permit of their being discharged from hospital and of free association with healthy people."

Brown et al. (1958) pointed out that, apart from the clinical state of the patient on discharge and his success in securing employment, the finding of suitable accommodation was of paramount importance. It is unreasonable to expect a patient who has spent many years in the artificial atmosphere of hospital to settle immediately in the community when he obtains employment. As the industrial training of a patient may take a considerable time, so too may his social training. Together with industrial training and resettlement must go social rehabilitation. Clark and Cooper (1960) describe an experiment in Cambridge which they call a psychiatric halfway house.

Their hostel was financed by S.O.S., a charitable organisation (with aid from the Cambridge Mental Welfare Association and the county council). They conclude that such a house is of value to a limited group of people and suggest that, for a catchment area of 360,000, 16 places would be adequate. They chose only patients who were in work or capable of finding employment within a month and who were deemed capable of achieving independent social life (in lodgings at least) within six months. Possibly these requirements are rather rigid, and if they were more flexible, there might be more patients suitable for admission; but it speaks well for the selection that 10 out of 19 schizophrenics were discharged in the first year.

Especially in view of the Mental Health Act (1959), I consider that the social reorientation and re-education of patients should be undertaken jointly by the hospital and local authority. In Bristol we have discussed possibilities with representatives of the housing and the health committee. I would like to see developed on the hospital estate (but removed completely from the hospital—on the opposite side of a main road) a row of 6–8 standard council houses such as patients may expect to live in on discharge; these houses would be built by the local authority and be jointly administered by hospital and local authority. With a minimum of supervision—e.g., a male nurse and his wife in one of the houses—discharged patients still undergoing industrial rehabilitation would occupy these houses as tenants, paying rent and learning again how to live socially acceptable lives. These proposals are still in the embryo stage; but the hospital management committee favour the scheme, as does the chairman of the local authority's housing committee.

If such a scheme of industrial and social rehabilitation were supported by the goodwill of the great national voluntary organisations, then at last there would be some real hope for the successful reintegration of the long-stay patient into the community.

My thanks are due to those people whose goodwill and enthusiasm have made this experiment possible—particularly to Mr. John P. Turley, director of Messrs. Tallon Ltd., and managing director of I.T.O. (Bristol) Ltd., without whom the project would not have come into being.

REFERENCES

Brown, G. W., Carstairs, G. M., Topping, G. G. (1958) *Lancet*, ii, 685.
Charlton, E. P. H. (1959) The Place of Work in the Treatment of Mental Disorder; p. 29. London.
Clark, D. H., Cooper, L. W. (1960) *Lancet*, i, 588.
Medical Research Council (1959) Report for the Year 1957–58. H.M. Stationery Office.
Ministry of Health (1958) Memorandum of Recovery of Part Cost from Hospital Patients going out to Work. H.M. (58) 72.
Ministry of Health (1959) Memorandum on the Rehabilitation of the sick and injured.
National Insurance Advisory Committee (1960) Report on the Question of Long-Term Hospital Patients. H.M. Stationery Office.
Stanley, R. (1959) The Place of Work in the Treatment of Mental Disorder; p. 39. London.

Medical Education

FAMILY STUDIES BY STUDENTS

Innovations at Lucknow

B. G. PRASAD
M.D. Lucknow, D.P.H., D.T.M.
PROFESSOR AND HEAD OF THE DEPARTMENT OF SOCIAL AND PREVENTIVE MEDICINE, KING GEORGE'S MEDICAL COLLEGE, LUCKNOW, INDIA

THE undergraduate student should see health and disease in their natural setting. This helps him to learn to look beyond the individual patient, to the family in which that patient lives, to his work and play, and to his social and cultural background. The student has to realise that the unit of his work is the family—not merely the sick person who first appears at the clinic.

In India the undergraduate curriculum is overloaded with diagnostic and therapeutic medicine of the hospital type. Few colleges give the student opportunities to work and observe in health centres, or with general practitioners or in families. He remains so preoccupied with clinical and laboratory findings that he gives little thought to the human, psychological, biological, physical, and social factors operating in the family or in the community. In medical education, therefore, provision has to be made for the study of man in disease in addition to the usual study of disease in man.

One of the suggestions made at the 1959 W.H.O. conference on mental health was that students should follow one family through health and disease over a number of years.[1] Departments of social and preventive medicine can suitably take the initiative in such a family-study programme.

HOW AND WHEN

At Lucknow the teaching of social and preventive medicine is spread over the preclinical and clinical years. A rural health centre at Sarojini Nagar is being developed to give field training to undergraduates and preregistration graduates, and a family-study programme is being introduced for the undergraduates. At present we have a five-year course (after intermediate science examination in physics, chemistry, and biology has been passed) and during his third and fourth years the student acts as family adviser to two families—one family with a mother and a growing child and another family with a case of a chronic disease. The study will help the student (1) to get a better understanding of the relation of health and disease to the total life of the family, (2) to observe normal growth and development and any departure from it, and also the means for maintaining normal health, and (3) to appreciate the economic, social, and emotional situations created by disease and disability. The department has on its staff a medical social worker to help and guide the students in this programme.

Some recommend [2 3] that students in their preclinical years should be given families for study; but this is not generally favoured in India [4] and I think it inadvisable. The student's average age on entry in 1959–60 was 19·7 for men students and 18·3 years for women, and at this age they are not mature enough to create and maintain good rapport with the families. They would not be able to give the medical advice, or arrange the medical relief for which the families would ask; yet they might start playing the role of a doctor, which would be undesirable both for them and for the family.

In the preclinical years it is better to give some introductory lectures and then hold clinical conference demonstrations (as is now done in Lucknow once a month [5]) at which selected patients are presented with their families, in cooperation with other departments. Such a conference is essentially "preclinical"—i.e., it is concerned with the circumstances and condition of the patient more than with his disease. In the analysis with which the conference concludes the chain of causation is examined to show where this could have been broken The aim is to lead students to think in terms of maintaining normal health, of the social causes operating in disease, and of the need for prevention, early detection, and early treatment.

A SUCCESSFUL PROJECT

In 1958 and 1959 the fourth-year students at Lucknow, who number about 160 per year, were each allotted a family having a registered case of pulmonary tuberculosis and were asked to write a medical and social history of the case. Before they did this they were given a schedule of study showing what information they must seek, and they attended a demonstration at which a case was presented in accordance with this schedule. Health visitors from the tuberculosis department introduced the students to the families, and the students consulted the departmental records of the cases. Each case-history was evaluated by me and the student was called to clarify points in the history and discuss the study. Occasionally he was asked to revisit the family or consult the records again.

The students on the whole did an excellent job, and some made instructive sketches to show the environment in which the families were living. Their interest was not confined to writing the medicosocial case-histories: where necessary they examined the sputum of patients and contacts, and took the contacts to the tuberculosis clinic for screening, Mantoux testing, and B.C.G. vaccination. A few patients who had defaulted from the clinic were persuaded by the students to revisit it for the usual check-up. Some of the students, going beyond their task, visited the neighbouring families to find out whether there were other cases of tuberculosis and what was being done for them.

I am grateful to Mrs. S. B. Nayar, medical social worker of this department, for helping in the preparation of the schedule of family study, and to Prof. A. Leslie Banks, W.H.O. visiting professor in social and preventive medicine at this college, for his suggestions and encouragement.

1. World Health Organisation Conference on Mental Health, Helsinki. Abstr. *J. Ind. med. Ass.* 1959, **33**, 196.
2. Gour, K. N. *Ind. J. publ. Hlth*, 1958, **2**, 40.
3. Vengsarkar, S. G. *ibid.* p. 245.
4. Patnaik, K. C., Holmes, E. M. *ibid.* 1959, **3**, 269.
5. Prasad, B. G. *J. King George's med. Coll. clin. Soc.* 1959, **42**, 1.

Public Health

MILK COMPOSITION

AN interdepartmental committee was appointed in May, 1958, under the chairmanship of Dr. J. W. Cook, vice-chancellor of Exeter University, "to consider the composition of milk sold off farms in the United Kingdom from the standpoint both of human nutrition and of animal husbandry and to recommend any legislative or other changes that may be desirable". Its report was published last week.[1]

LEGAL DEFINITION

The committee finds that the definition of milk in the Food and Drugs Act (1955) is inadequate in relation to milk composition. The suggested statutory definition is:

'Cows' milk' means the secretion, excluding colostrum, which can be gained by normal milking methods from the lactating mammary gland of the healthy, normally fed cow.

RECOMMENDATIONS

The committee's main conclusions and recommendations are as follows:

Because milk is important in the human diet particularly by virtue of its content of solids other than fat (referred to collectively as S.N.F.), the consumption of milk S.N.F. should be maintained and, if possible, increased. Small changes in the fat fraction of milk are less important nutritionally than changes in S.N.F. The evidence of a link between either atheroma or ischæmic heart-disease and the consumption of milk fat, though suggestive, is not conclusive, and much research into the problem is urgently needed.

Both the fat and S.N.F. contents of milk have been falling gradually over the past thirty years in England and Wales, though there has been little change in Scotland. The decline in S.N.F. may continue unless steps are taken to arrest it, but most milk producers could improve the composition of their supply by changes in herd management if they were given the incentive.

The dairying industry therefore should aim not only to maintain but also to improve the S.N.F. content of liquid milk, and both statutory and marketing means should be used to this end.

1. Milk Composition in the United Kingdom. Cmnd. 1147. H.M. Stationery Office. 1960. Pp. 92. 5*s*.

Milk should continue to be sold as it comes from the cow, except for separated and other special grades, which should be clearly labelled and controlled. As a first step towards improving the quality of milk the marketing boards in Great Britain should pay less than the normal price for milk which is deficient in S.N.F. If this proposal is adopted the composition of milk from individual farms must be tested regularly by the dairy or depot to which it is first consigned.

Fixed legal minimum standards for fat and S.N.F. contents of milk would protect the consumer. The present standards are designed to ensure that milk is genuine, but they do not prevent the sale of genuine milk of low composition. The fat and S.N.F. contents should continue to be the criteria used for both legal and marketing purposes, and consideration should be given, within ten years, to prohibiting the sale of whole milk containing less than 3% fat or 8·5% S.N.F. The Hortvet test (for freezing-point depression) should, with certain provisos, be accepted legally as proof of addition of water to milk samples. Abstraction of fat from milk intended for sale as whole milk should be made a specific legal offence.

Milk recording should cover S.N.F. as well as fat content, because it is important to have details of the S.N.F. performance of individual animals if milk producers are to manage their herds to the best advantage. As soon as adequate information is available, S.N.F. records should be included among the data considered in the selection of bulls for artificial insemination. Licences for bulls of the dairy breeds should be refused in the absence of satisfactory records, and a new category of superior or premier grade should be introduced to include a minimum S.N.F. performance.

Diphtheria in Derby

A girl of 11 who lived in the Castle area of Derby fell ill with tonsillitis on Aug. 19. All throat swabs proved negative for diphtheria, but she died on Sept. 1 and the cause of death was established as myocarditis due to diphtheria. On Sept 8, her brother of 13 was admitted to hospital with diphtheria and another brother was admitted as a carrier; and next day her mother and father were also admitted as carriers. On Sept. 10 a girl of 4 and on Sept. 14 a boy of 9 also living in the Castle area went into hospital with diphtheria. By Sept. 23 one other carrier had been identified and two cases of "diphtheroids". Virulence tests were being performed. None of the children with diphtheria and none of the carriers had been immunised.

Bovine Tuberculosis

An order made this week by the Minister of Agriculture declares the whole of England to be, from Oct. 1, an "attested" area in which all herds are tested for freedom from tuberculosis.[1] Scotland and Wales became attested areas last October. During an informal ceremony at the Ministry on Sept. 26, the Minister, Mr. Christopher Soames, said the completion of the eradication plan was a considerable achievement brought about by intimate cooperation between the Government veterinary services on one side and the farmers and private veterinary surgeons on the other. Mr. J. W. Salter Chalker, chairman of the animal health committee of the National Farmers' Union, hoped that a similar attack could now be made on other diseases—notably swine fever and contagious abortion.

First-aid in Factories

IN future those nominated under the Factories Acts to be in charge of first-aid boxes in factories with more than 50 workers will have to be registered nurses, enrolled assistant nurses, or holders of a certificate of first-aid issued within the previous three years by a designated training organisation. An Order [2] to this effect will come into force on July 1, 1961; but until the end of 1962 a person shall be deemed to be properly trained if at any time in the ten years preceding the date when the Order was made (Sept. 13, 1960) he has held a certificate in first-aid issued by a training organisation.

1. *Times*, Sept. 27.
2. First-aid (Standard of Training) Order, 1960. S.I. 1960, no. 1612.

In England Now

A Running Commentary by Peripatetic Correspondents

THE Borough Surveyor thought that three people were buried there. Only three names were carved on the solitary tombstone that stood in the way of his scheme to widen the corner by the chapel. There had been too many fatal accidents to leave it any longer. All he wanted to do was to chop off a triangle of land which he thought must have been part of the highway before the footpath was laid in Victorian times. Although nobody locally seemed to care, we got a licence from the Home Office to open the marked grave and move any human remains to the public cemetery. The Borough Surveyor thought it would be all over by breakfast time, but sent me an invitation. Medical officers of health are supposed to do their best for the safety of exhumations, so I went along.

The grave was 120 years old and contained a lot of babies' bones as well as the three adult skeletons. We put them all carefully into new caskets and sent them off to the cemetery. Then the soil slipped a bit and we realised that there were more on either side. We filled in the grave and summoned a full-scale conference on what to do next. The new road surface was going to be 3 ft. lower than the old footpath, and claims were coming in from the electricity board, the gas board, the water department, the Post Office telephones, and the drainage staff, all to lay their weird paraphernalia under the new highway line, and the usual right to dig it up again whenever they pleased. We reckoned that they might get well down into the grave levels, and we dare not risk a scandal. Nobody knew how many people had been buried in that strip of land over 100 years ago: the chapel registers were no help. The Borough Surveyor thought there might be three or four more to move, so up went the screens again, and the single-line traffic: the workmen started to dig in odd spots. When the first day yielded results scattered all over the site, we were faced with no alternative but to settle down for the summer and deal with the area like an archæological excavation.

We got out 134 bodies all told. They were not without medical interest. A couple of dozen had been buried in quicklime: smallpox, cholera, and typhus were common in the town in those days. One skeleton had no head, and another had its skull stove in. Adult teeth were very good on the whole, and we did not see much evidence of rickets. Some of the graves contained as many as 7 adult skeletons laid one on top of another, with odd bundles of infant bones tucked around their feet. Not a sign of wedding rings, and the only trinket was a little silver medallion commemorating the accession of William IV and Queen Adelaide. The site is now filled in, the lamp-posts up, the tarmac laid, the white lines painted, the double-deckers rumble by. I can only hope that the 134 forgive us for disturbing their rest. We did not like it either.

* * *

Gently it slithered through my letter-box. "Depression", it announced on the front (all my advertisements seem to say this now) and within snuggled a slim provocative little disc which, at 33 per minute, offered a moving dialogue between an inquisitive G.P. and a calmly instructive Consultant Psychiatrist. Some good straightforward facts and a wonderfully oversimplified classification filtered through two short sides of synthetic conversation, after which the G.P. presumably went his way rejoicing and cured everybody. But at least no excessive claims were made and (unlike some recent advertisements) a wise limit was set on which depressions the G.P. should treat and which he should send to a Consultant.

It is not this inoffensive record, but the future prospect that appals me. At first as a gimmick it will be popular, then people will realise that you can read things more quickly than playing them over *and*, if you like, listen to Beethoven at the same time. Then the discs will need to sustain themselves with gimmick upon gimmick. "Special offers" perhaps will be announced at some point during the playing; some firms may vocalise theirs; others trying blank-verse. Listening to them as they come will be a compulsive ritual just to find out what they are up to this

morning—and remember, you can't flick a record over like a booklet. It means sitting there for 9½ minutes or else trying to decipher the gabble at 45, which probably plays hell with the stylus.

I suppose the thing is useful for people who have failing vision or who cannot read, but I can't say it brightened my morning.

* * *

I have been offered the following translation of a Russian article:

Hard fall out symptoms in area of autonomic nervous system as a later consequences after poliomyelitis

"Till now poliomyelitis was considered as a desease of spinal cord by causing a damage in prior horns of spinal cord and subsequently the clinical symptoms shows a diminished or output of motorical innervations in various groups of muscles or in uper or lower extremities according to the localisation and extension of pathological substratum. Contrary this article proofs that not only the motorical system is damaged but throughout an appropriative autonomic nervous system can be devastated by an extended pathological substratum of poliomyelitis.

"According to these insufficiencies we must concluse that pathological substratum by its extension damaged not only a prior horns, but in neighbourhood dislocated a side cords as a higher centers of autonomic nervous system. This an explanation of nine abortus and a great œdemas of lower extremities from which organs (an uterus and lower extremities) has their higher centers of autonomic nervous system in region where poliomyelitis made a biggest devastation in area of lumbar I-V.

"Such an observation in literature till now was not confirmed or noticed."

I'll say it wasn't!

* * *

"Resourcefulness is a dominant gene in my family," said Ananias, levering Boyd's *Pathology* out of the bookcase to see whether the gin bottle was behind it. "A prize example was my cousin Arthur. He landed in the United States without a penny and six weeks later he was worth $5000—at any rate that's what the police were offering for him. I am not therefore downcast because some abandoned bodysnatcher has finished the gin. I shall simply put some adhesive plaster over my antecubital fossa and lie on a couch in the blood-transfusion centre. Light refreshments will be brought to me by ravishingly beautiful nurses—they keep the prettiest ones there to bait the trap—and I'm all set for a date at the Palais, if you've got any money. Incidentally, *have* you got any money?"

"Yes thank you," said Macabre, the pathologist, "and don't tell me your Chief has sent you here to request even more bottles of blood. Is he keeping up with the Draculas or something?"

"My Chief, the Laird MacGrolloch, was muttering about Flodden Field last night. When he does that, the next patient he broaches needs a refill, even if he, or she, has only had their ears pierced. So please attend to my order now before the flowers of the forest are a' wede awae, and for goodness' sake ensure that your tame ghouls get the bottles from the correct bin, because I heard of one patient who received some from a Chinaman. He became *ipso facto* a blood-brother in the Mildewed Lotus Tong, and every time Tong warfare broke out he had to have police protection."

"I don't care whether it's for the flowers of the forest or Bonnie Prince Charlie," said Macabre crossly, "the stuff costs the country about £30 a pint. You could," he added hopefully, "be dead and buried for less than that."

"My cousin Arthur nearly was," replied Ananias. "He's suing the pathologist for giving him cirrhosis of the liver. Seems he forgot to crossmatch the blood for the various brands of gin."

* * *

APOTHECARIES ABANDONED

To ease the task of future pupils
Let grains ingrain'd no longer be
Abandon minims, have no scruples.
Come, take a drachm—no, dram—with me.

Letters to the Editor

OUR POOR THAMES

SIR,—Compared with Our Poor Thames the Tone is an insignificant stream with an average daily flow in summer of about 15 million gallons but suitable in many places for alfresco bathing. It drains a district heavily stocked with animals and receives treated and untreated human sewage. Since 1955 this laboratory has examined daily or weekly samples of water from the Tone for *salmonella spp.* using both the Moore swab and (less often) a filtration method. Our results have been thus:

Year	*Samples*	*Isolations*
1955	82	13
1956	134	6
1957	60	0
1958	32	1

During this period many people have bathed at or below the sampling point. It is impossible to say that no-one has acquired an infection from bathing during this period, but this laboratory (to which almost all the bacteriological specimens from this neighbourhood are sent) has seen no evidence of such infection.

I hesitate to mention my personal experience because I do not want to be accused of foolhardiness. At one time I lived on the banks of the Tone and in hot weather my family bathed in it regularly. During one hot spell my wife, my daughter, my spaniel, and I bathed every evening for about a week. At this time *Salmonella thompson* could be found in every Moore swab put in the river at our bathing place and for 8 miles upstream. None of us made any particular effort to keep the water out of our mouths but none of us had any symptoms of illness. I did not examine our fæces bacteriologically as I should have done.

There is not much evidence on the dose of salmonellæ necessary to produce disease in man, but such as there is suggests something of the order of 10^6 organisms [1]: (the figure for *Salm. typhi* is probably much less). Using a filtration method of isolation (suggested to me by Dr. G. J. G. King) some rough estimates of the numbers of salmonellæ present in the Tone water on several occasions gave figures of 10 organisms per litre or less. I have no doubt that salmonella infections can be acquired by bathing in rivers—but very rarely. I would, however, avoid bathing immediately below a sewage outfall.

Public Health Laboratory,
Taunton. J. A. BOYCOTT.

ECZEMA VACCINATUM

SIR,—Dr. Reynolds does well to remind us, in his article last week, that this infection often proves fatal in infants and can be prevented; but he does less than justice to his own countrymen's work on the subject, for in quoting eighteen references he mentions only two British. I append a list [2–14] of some of the more important British papers on Kaposi's varicelliform eruption.

McLachlan and Gillespie [2] described a severe outbreak of vaccinia infection in a Glasgow children's ward; and Brain and

1. McCullough, N. B., Eisele, C. W. *J. infect. Dis.* 1951, **88**, 278.
2. McLachlan, A. D., Gillespie, M. *Brit. J. Derm.* 1936, **48**, 337.
3. Brain, R. T., Lewis, B. *ibid.* 1937, **49**, 551.
4. Whittle, C. H., Lyell, A., Miles, J. A. R., Stoker, M. G. P. *ibid.* 1950, **62**, 195.
5. Leverton, I. C. S., Whitlock, F. A. *ibid.* 1949, **61**, 170.
6. Anderson, T. *ibid.* p. 157.
7. Bettley, F. R. *ibid.* 1940, **52**, 222.
8. Brain, R. T. *Aust. J. Derm.* 1954, **2**, 109.
9. Brain, R. T., Dudgeon, J. A., Philpott, M. G. *Brit. J. Derm.* 1950, **62**, 203.
10. Brown, W. H. *ibid.* 1934, **46**, 1.
11. Ellis, F. A. *ibid.* 1936, **48**, 524.
12. McLachlan, A. D. *ibid.* 1934, **46**, 8.
13. Somerville, J., Napier, W., Dick, A. *ibid.* 1951, **63**, 203.
14. Varley, R., Kletz, T. *ibid.* 1949, **61**, 166.

Lewis [3] succeeded in producing lesions with blister fluid by inoculating a rabbit's cornea. Full virus studies were published for the first time in this country [4] in 1950, and in a review of 58 cases of Kaposi's varicelliform eruption in the literature 27 were found to be due to vaccinia and 11 to herpes-simplex virus. Other viruses such as the influenza virus might produce the same clinical picture [5] and could account for some of the remaining 20 cases in which the virus was not traced. Anderson,[6] to avoid confusion, suggests the name "virus pyodermia" because more than one virus is implicated.

Vaccinia infections of this type can occur in adults and, as Dr. Reynolds suggests, atopic eczema is not the sole portal of entry for the virus. Of 3 adults I have seen with vaccinial lesions of this type one was an army recruit whose eruption appeared, about ten days after his primary vaccination, not on eczematous lesions, because he had none, but on chronic patches of psoriasis. He was very ill for a week or two but survived.

Cambridge. C. HOWARD WHITTLE.

TROLLEY-SETTING

SIR,—Dr. Behr (Sept. 17) wonders whether General Nursing Council examiners can be persuaded to accept new techniques for dressing wounds. In Sunderland many of the methods advocated by him have been used for two years.[15–17] Bowls and gallipots are not used for dressings and each dressing is done from an individual pack; this eliminates the old type of trolley setting.

Dr. Behr need have no misgivings. All G.N.C. examiners who have seen this method have accepted it at once and have welcomed it as an improvement in nursing technique.

Central Laboratory, Royal Infirmary, Sunderland. J. F. WILSON.

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—I should like to thank Dr. Lawrence for his reply (Aug. 27) to my letter of Aug. 13. His criticisms are welcome but not unexpected.

I fully realise the theoretical dangers that a syringe which is sterilised only once every three months is liable to become contaminated. I have always assumed that the small quantity of preservative that is mixed with all types of insulin will maintain the sterility of the plunger and inner surface of the barrel of the syringe as well as the needle. As the syringe is never rinsed in spirit or water, a trace of the preservative will remain constantly in the syringe and needle. Whatever the theoretical dangers I have no doubts about the practical safety of the method. Seventeen years' trial involving over six thousand self-administered injections without ever a trace of inflammation seems sufficiently satisfactory a result to suggest that other diabetics might like to experiment along the same lines.

Dr. Lawrence considers that many patients would not observe the "no-touch" technique which I recommend for the needle, but I think he is unduly pessimistic. In my experience, the most likely time for contamination is in assembling the syringe and needle after sterilisation by boiling. If a diabetic can perform this manœuvre correctly, there is no reason why he should not be able to avoid touching the needle during his daily injections. I can only remember making this error twice.

I am afraid Dr. Cuddigan (Sept. 3) must have misread my letter concerning the use of surgical spirit. The syringe is never placed in spirit, nor is it rinsed in water except immediately before resterilisation when the old needle becomes too blunt for comfort and is replaced by a new one.

Mr. Merryweather Shaw rightly draws attention (Sept. 3) to an omission I made in describing the loading of the syringe with insulin. It is of course important to inject air into the inverted bottle before withdrawing insulin in order to avoid producing a vacuum in the bottle, but the risk of contamination appears to be of theoretical rather than practical significance. Mr. Shaw's use of sterile, disposable, plastic syringes may sound somewhat extravagant, but Dr. Lerman (Sept. 17) points out that these syringes can be produced at a very low cost. However, as a glass syringe should last several years (I am still using my fourth), the cost of plastic syringes will have to be extremely low to make their use on a large scale an economic proposition.

Finally, I was delighted to read Dr. Wauchope's letter (Sept. 10). She obviously treats her injections of insulin with an even greater care-free abandon than I do. I have never quite reached the depths of non-sterility that she proclaims as I always swab with spirit the rubber cap of the bottle as well as the site selected for injection, but her technique (or lack of it) over many years has given complete satisfaction. I hesitate to accept her theory that diabetics develop an immunity to their own contaminants. In theory there is great risk of infection by using a technique that involves such infrequent sterilisation of one's syringe, but apparently this does not manifest itself in practice.

Queen Elizabeth Hospital, Khormaksar, Aden. F. STEPHEN CARTER.

VIRUS TUMOURS OF MICE

SIR,—After reading your occasional survey [1] we should like to record that one of our observations [2] still awaiting explanation was as follows:

About 40% malignancy—i.e., different tumours and stem-cell leukæmia—developed among F_1 progeny of some low-malignancy strain mice, originally free of leukæmia, if mothers were inoculated subcutaneously with massive doses of A.K.R. lymphocytic leukæmic cells in their late pregnancy; and the same inoculations of pregnant A.K.R. mice, causing the death of mothers in acute leukæmia, failed to alter the fate of their A.K.R.–F_1 progeny.

Although these preliminary results await confirmation, we suggested that if these induced tumours or leukæmias in the low-malignancy strain were caused by a virus, it would be difficult to understand the absence of its effect (cf. Laterjet [3]) in the original A.K.R.-leukæmia strain.

Department of Medicine, University Medical School, Szeged, Hungary. E. KELEMEN M. TENYI.

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—The difference of opinion between Dr. Allchin (Sept. 17) and myself is, no doubt, very largely semantic.

What I believe the court to have requested, in the first place, is my advice in the form of a *practical recommendation*, in a specific case at a particular time; and if such a recommendation were to be made in the form of what I feel *ought* to be done (were it only possible to do so), I would not be assisting those who have sought my advice, in reaching a practical decision in that case and at that time. I would, therefore, be helping neither the individual concerned, nor society, nor the authorities and officials whose responsibility it is to take some immediate and positive action; I would also be most liable to discourage further cooperation on the part of the latter, who could hardly be blamed if they were then to conclude that psychiatrists were unrealistic and unhelpful. In my view, we would thus have defeated, ab initio, our own aims of achieving through the education of all those involved a better and more effective mental health service.

This is, therefore, far from saying that I in any way underestimate the importance of the educational duty of the psychiatrist, as emphasised by Dr. Allchin. In fact, I too have long made it an invariable practice clearly to state the action, method of treatment or care, which would, in my

15. See *Lancet*, 1960, i, 661.
16. *ibid.* Aug. 13, 1960, p. 353.
17. Thompson, M. E. *Nursing Times*, 1960, **56**, 869.

1. *Lancet*, July 23, 1960, p. 200.
2. Kelemen, E. 7th European Congress of Hæmatology, London, 1959.
3. Laterjet, R. Ciba Symposium on Carcinogenesis; pp. 274–295. London, 1959.

opinion, ideally be required: but, unfortunately, that is most frequently something quite distinct from the practical recommendation for which I am asked. Indeed, I may be fully convinced that a patient is in very great need of six months' rest in a beautiful climate, but I—and he—must needs compromise with some less satisfactory " solution ", and will most probably have to go on doing so in the foreseeable future, and, it may be, until the advent of the millennium.

Bransgore, Hampshire. R. H. AHRENFELDT.

ÆTIOLOGY OF ECLAMPSIA

SIR,—Moses et al.[1] claimed that the development of pre-eclampsia in a patient both of whose adrenals had been removed, apparently for Cushing's syndrome, is " further evidence that the adrenal steroids do not play a major role in the causation of pre-eclampsia ".

I would respectfully submit that the case described was not pre-eclampsia but chronic hypertension. Her blood-pressure at the beginning of pregnancy was 170/110 mm. Hg. At about the 6th month it was 220/110 when she had headaches, nausea, vomiting, malaise, and albuminuria, which might well be attributed to a superimposed pre-eclampsia. Throughout her pregnancy, however, she had been receiving hydrocortisone. Is it certain that this had nothing to do with the rise of blood-pressure, œdema, and albuminuria, thus stimulating pre-eclampsia or actually causing it?

Moses et al. quote Cohen [2] as reporting the onset of pre-eclampsia in a woman who had Addison's disease. But this patient also was receiving adrenocortical therapy throughout her pregnancy.

Both these cases must therefore be rejected as evidence against the role of the adrenal steroids in the ætiology of pre-eclamptic toxæmia.

Wollstonecraft, New South Wales. F. J. BROWNE.

THE VERY DEAF CHILD

SIR,—Your annotation of Sept. 17 must not go unchallenged, for some of your statements may mislead those who have had little experience of the deaf child and its problems.

The Board of Education Committee's classification, though written in 1938, has not yet been superseded for the good reason that no-one has been able to formulate one with less defects and more practical advantages. As with all definitions, no harm can come from a theoretically poor classification provided the parameters involved are understood, and educational and administrative elasticity is maintained. The National College of Teachers of the Deaf has recently given time and thought to this classification, and members to whom I have spoken do not regard it as sacrosanct, but do not minimise the difficulties involved. These difficulties are due to an inability to define, in any mathematical way, such terms as " partial deafness ", " good lip-reading ability ", " spontaneous speech ", and " adequate auditory stimuli ". When experimental methods and applied psychology have given us better means of measuring these concepts, we may be able to rewrite the existing classifications.

Damnation of schools for the deaf in your last sentence is unjust. It is true that there are bad schools but there are good ones too, and the same range of quality is found in schools for the deaf as in schools for normal children. While heartening results have been achieved in recent years by the treatment of many children as partially deaf rather than as grade III, it must not be forgotten that there are still oral failures in the best schools, and that there are children who do not learn to speak at all, despite all the advantages of an early start and every possible help. Teachers of the deaf are as aware of their failures as, for instance, is the honest surgeon of his recurrent hernias or the otologist of his unsuccessful fenestration operations, but these failures do not make admission to hospital and operative treatment " unthinkable ".

It is very right that recent results achieved by auditory training, in the case of young children, should be given wide publicity, but it must be remembered that there has not yet been any suitable statistical survey of the long-term effect of this early training to show that lip reading, which incidentally was not mentioned in your annotation, can be discarded as an educational method, or that the failures of auditory training are unknown.

Eye, Ear and Throat Hospital, Murivance, Shrewsbury. E. N. OWEN.

PORPHYRIA

SIR,—Nazzaro, Topi, and Venerando [1] suggest that the form of porphyria designated porphyria cutanea tarda should more appropriately be named mixed or combined porphyria on the grounds that many of these patients present both cutaneous lesions and the systemic symptoms characteristic of acute porphyria. They also comment that in some instances there is evidence of familial incidence whilst in others this is wanting even though relations are available for examination.

Dean and Barnes [2] have shown that the classical intermittent acute porphyria (I) can be differentiated on biochemical grounds from an apparently mixed form for which they suggest the name porphyria variegata (II). Both these forms are based on constitutional predispositions which are inherited according to the mendelian dominant rule with no sex-linkage. Porphyria variegata is a specific entity and should not be named or regarded as a mixed or combined form. Barnes [3] has also reported the prevalence in Bantu subjects (indigenous Africans) of a cutaneous porphyria (III) in which there is no tendency to acute episodes and which can be distinguished from erythropoietic (congenital) porphyria. There is no satisfactory evidence for an hereditary basis for this form. In summary, the distinguishing features of these three forms are:

(I) *True acute porphyria.*—Raised urinary excretion of δ-aminolævulic acid and porphobilinogen is the most constant characteristic. This sometimes occurs in latent (presymptomatic) cases, is exaggerated during the acute episodes, and persists for long periods after recovery. Stool porphyrins are sometimes normal, sometimes slightly increased, but, according to present limited experience, never markedly increased.

(II) *Variegate porphyria.*—The most constant biochemical anomaly is a large increase in stool porphyrins which is found irrespective of the clinical status of the patient and has been observed in asymptomatic members of affected families. δ-aminolævulic acid and porphobilinogen are excreted in excess during acute attacks but diminish with recovery and are almost invariably normal during remission from attacks. Porphyrin is sometimes normal in the urine during remission, but traces or larger amounts can usually be detected.

(III) *Cutaneous porphyria.*—Urinary porphyrins (mainly uro-) are present in excess in freshly passed urine. This is most pronounced when skin lesions are active but slight excesses have been observed some years later when scarring was the only evidence of former lesions. δ-aminolævulic acid and porphobilinogen are usually normal but slight increases have been found when uroporphyrin excretion is very high. Stool porphyrins are normal in about half the patients and only slightly raised in the remainder.

Many cases of porphyria have been reported in Italy, Spain, and France, both cutaneous and acute symptoms being mentioned, but very little of this literature is available to us. If, as may be inferred from the statement by Nazzaro et al., many of these patients have variegate porphyria, the interesting possibility arises that while true acute porphyria has originated in Northern Europe (Lapland is suggested by Waldenström [4]) the variegate form may have been established in the south. Both these hereditary types have been carried by travellers and migrants to other countries in the world. The picture is complicated by the probably acquired cutaneous porphyria

1. Moses, A. M., Lobotsky, J., Lloyd, C. W. *J. clin. Endocrin.* 1959, **19**, 987.
2. Cohen, M. *Arch. intern. Med.* 1948, **81**, 879.

1. Nazzaro, P., Topi, G. C., Venerando, A. *Policlinico*, 1958, **56**, 1243.
2. Dean, G., Barnes, H. D. *S. Afr. med. J.* 1959, **33**, 246.
3. Barnes, H. D. *ibid.* p. 274.
4. Waldenström, J. *Acta genet.* 1956, **6**, 122.

(III). Alcohol and arsenic (anti-syphilitic treatment) figure prominently among suggested ætiological factors,[5–7] but these probably include liver noxa of many kinds and contributory liver damage consequent upon earlier illnesses cannot be ignored. Such cases may, therefore, arise sporadically. Exposure to sunshine is probably an evocative agent for the skin lesions in groups II and III, but this has been included with alcohol and heavy metals as a primary ætiological factor by Ippen.[8]

Accurate differentiation of these forms, especially between II and III, is not merely an academic exercise. Patients in groups I and II are susceptible to acute episodes which might end fatally, while, according to present experience, those in group III are not. There are on record many instances of these acute manifestations being precipitated by the use of barbiturates, including thiopentone for anæsthesia, and other drugs. It is thus very desirable that these cases should be fully investigated.

H. D. BARNES
L. C. TURCHETTI TUCCIMEI.

Johannesburg.

VOLUNTARY ISOLATION

SIR,—Having had close experience of 85 separate groups at work in the Antarctic over the past 11 years I was interested to read an extract from your annotation [9] on this subject.

Only three weeks earlier I had written a letter to one of our scientific advisers in England in which I said that ability and qualifications were "75% of the necessary background to successful living on a base. It does not matter how active and strong and cheerful a man is, if he cannot keep the engines running, or the base on the air, then the others will have no time for him and he himself will lose his self-respect, a state which readily gives rise to neurosis." This bears out the statement that "The overriding criterion is that a man should be efficient at his job". We have also had a few, fortunately very few, perfect examples of the "type of newly graduated scientist, unworldly but intellectually arrogant".

J. R. GREEN
Secretary,
Falkland Islands Dependencies Survey.

Port Stanley,
Falkland Islands.

PSYCHOANALYSIS

SIR,—In the preface to the 1960 edition of *Clinical Psychiatry*, Dr. Mayer-Gross complains that his detailed critique of psychoanalysis in the introduction to his book in 1954 was not challenged. Two reasons at once come to mind:

(1) Readers of psychiatric literature, perhaps more than those in other fields, are very selective, and generally read only the publications of kindred minds. I think this would also itself explain his contention that the attempted re-export of psychoanalytic teaching from America into Europe was "largely in its original naive form". By 1954, the body of psychoanalytic work pursued in America is greatly modified in form from orthodox psychoanalysis, although this still had its champions, perhaps proportionately more in England than in America.

(2) The grounds for criticism were also ancient in derivation. In fact, in the chapter on the psychological treatment of schizophrenia in the 1960 edition, Speer (1927) is still quoted as having arrived at the judgment that psychoanalytic methods leave the patient unaffected by treatment.

American psychiatry today is greatly influenced by the works of Harry Stack Sullivan, Frieda Froom-Reichmann, Clara Thompson, and Carl Rogers, to mention a few, none of whom are even mentioned in his references.

M. J. ORTEGA.

Littlemore Hospital,
Oxford.

5. Brunsting, L. A. *A.M.A. Arch. Derm. Syph.* 1954, **70**, 551.
6. Berman, J., Bielicky, T. *Dermatologica*, 1956, **113**, 78.
7. Tappeiner, S. *Wien. klin. Wschr.* 1953, **65**, 143.
8. Ippen, H. *Berufsdermatosen.* 1959, **7**, 256.
9. *Lancet*, 1960, i, 1231.

SHORTAGE OF DIETITIANS

SIR,—We are very interested in your annotation of Sept. 17 on the shortage of dietitians. I write, however, to point out that integrated courses of training for dietitians lasting three years have already been established.

A course of three years, including six months at a recognised hospital dietetic department, has been in existence for some years at the Battersea College of Technology. The requirements for entry include chemistry and either physics or biology (or zoology) at advanced level in the General Certificate of Education. A four-year integrated course has just been instituted at the Leeds College of Technology, and candidates with advanced-level chemistry and biology may be admitted directly to the second year—that is, for a three-year course.

B. J. JAMIESON
Secretary, The British Dietetic Association.

London, S.W.3.

*** We are grateful to Miss Jamieson for this information, and also for sending us a copy of the report [1] of a fact-finding committee set up last year by the British Dietetic Association. 740 questionaries were sent to dietitians, and in the 391 returned the great majority expressed dissatisfaction with the present situation. Frequent comments were made about poor salaries in the National Health Service, the length of training required, the lack of status in hospitals, and the misuse of dietitians' services.—ED. L.

CONTROL OF HOSPITAL CROSS-INFECTION

SIR,—I was interested to read the article of Sept. 10 by Professor Elek and Dr. Fleming on a new technique for the control of hospital cross-infection using BRL.1241 in a maternity unit, because I described [2] a rather similar technique in 1956 by which a successful attempt was made to reduce nasal infection in a residential nursery which catered for 20 children up to 3 years old.

The infection had been present for many months but responded in an amazing way to the use of 'Aeryl 4' in an electrically operated 'Phantomyser' spray. The results of this were assessed clinically, a successful result being shown by the disappearance by the 24th day of nasal discharge in 14 of the 17 babies involved.

The conclusions I drew from my investigations were:

(1) The infection had been maintained by infection of babies shortly after entering, and continual reinfection thereafter.

(2) The effects of the spray were mainly mechanical—i.e., in the formation of droplet nuclei carried down from the atmosphere to the floor.

(3) Although this was not an ideal method of dealing with the situation it was at any rate successful in this particular instance.

I was sorry to learn that the Medical Research Council had not found my method successful in dealing with infection in residential nurseries run by Dr. Barnardo's, though I suspect that the method they adopted entailed the use of a vaporiser instead of an atomiser.

I hope that the article by Professor Elek and Dr. Fleming will stimulate further interest in a method which I feel could play an important part in dealing with the problem of cross-infection in hospitals.

J. ADRIAN GILLET.

Civic Centre,
Dagenham.

1. *Nutrition*, 1960, **14**, no. 2.
2. *Med. Offr*, 1951, **86**, 5.

HYOSCINE ADDICTION AND INTOXICATION

SIR,—Hyoscine was used extensively for motion sickness in the Forces from 1942 onwards, and was first sold to the public in May, 1947, as 'Kwells'. The toxic effects of hyoscine may include confusion, a muttering delirium, or stupor deepening to coma.

A 54-year-old housewife was admitted to hospital on Aug. 14, 1959, in a confused state. She was agitated and frightened, and she was seeing "thin, horrid slug-like creatures with golden heads coming out of the floor". She was disorientated in space and time, and it was very difficult to hold her attention. There was clouding of consciousness, and her thinking was so confused that further history-taking was impossible.

Her husband stated that the trouble started after hysterectomy six years previously, when she began to feel nervous and depressed and to suffer from headaches for which she took a variety of tablets, mostly, he thought, sedatives. She had been buying kwells regularly for about two years to help her in travelling, but recently had been taking an increasing number of tablets even when not travelling. Six weeks before she had been discharged from another hospital where she had had a course of electroconvulsion therapy for a depressive illness. After this she had increased her consumption of kwells to 12 tablets daily.

Her face was leaden-grey, and her skin and mucous membranes were dry. The pulse was full and bounding, and the blood-pressure 160/90 mm. Hg. The pupils were dilated and fixed and all reflexes sluggish. There was no rash or skin disorder and the bladder was not distended. After admission she was given a course of intramuscular 'Parentrovite', prophylactic penicillin, and copious fluids. The atropine-like symptoms responded to neostigmine bromide 15 mg. three times a day.

Routine blood and urine investigations were normal. An electroencephalogram on the third day after admission showed "repeated episodes of theta activity which suggest organic disturbance. This appears to be in the deeper brain areas but is symmetrical on both sides which suggests this is a toxic rather than a space-occupying disturbance". The record was repeated fourteen days later and showed no abnormality.

The patient remained confused and disorientated for five days after admission, but next day she was no longer hallucinated, and was more cooperative, although she still showed some clouding of consciousness and incoherence of thought. Memory for recent events was impaired and there was a tendency to confabulate. After a further seven days she was completely rational and capable of giving a coherent history.

She had first started to take increasingly large doses of barbiturates after the hysterectomy six years before. Several times she changed her doctor after being refused the quantities of drugs she wanted, and at times she used other patients to obtain barbiturates for her. About two years ago she started taking kwells, at first for travel sickness, but later because they eased the tension she felt when she had to meet other people. In the few months before admission to hospital she was increasingly depressed and had had frequent headaches. She found it necessary to increase the number of tablets until shortly before admission she was taking 12 daily. Her degree of dependence was such that on one occasion, at a weekend, her husband had to tour the local chemists' shops to obtain fresh supplies for her.

Psychiatric evaluation indicated that she had a chronic anxiety hysteria with an overlay of neurotic depression.

Three weeks after admission she showed no signs of toxicity, and although she had been much brighter, her depression returned, and she became irritable and hypochondriacal. She was given a course of E.C.T. which cleared the depression. She left hospital for weekend leave on Oct. 2, 1959, and failed to return.

In spite of the sedative action of hyoscine, we have been unable to trace any recorded cases of addiction, and this case is reported to emphasise that substances other than the usually recognised drugs of addiction may lead to habituation in susceptible personalities.

There has recently been an increase in addiction to non-scheduled drugs—for example, to phenmetrazine ('Preludin'),[1 2] and to carbromal, chlorodyne, and phenmetrazine.[3] Many are in favour of restricting the sale of all such drugs, and this has been done for phenmetrazine. Douthwaite,[4] however, believes "we should think very carefully before recommending restrictions to legislators which would inevitably involve the practitioner in yet more work and which would do but little to protect a relatively small number of psychopaths", and we subscribed to this view. It would scarcely seem justified to restrict such a useful drug because of intoxication by addiction in a neurotic personality.

Our thanks are due to Dr. R. Mackarness, of E. Griffiths Hughes, Ltd., for his helpful advice.

Whittingham Hospital, Preston. P. HARPER
D. P. OAKLEY.

PARKING AND THE DISABLED DRIVER

SIR,—When I committed my most recent parking offence by exceeding the time-limit plainly indicated on a sign obscured by a furniture van, the heart of a constable softened at my suggestion that he might care to push my wheel-chair the odd five hundred yards to the nearest car park, when next I ventured to visit the police station. I had just called to settle a little matter arising from another recent parking offence.

The disabled motorist is obliged to do his best to avoid adding to the appalling traffic chaos, but his plight is never obvious until he attempts to extricate himself from his vehicle or shouts for help, the former often impossible and the latter liable to misinterpretation. His need to find a parking space close to the shop or house he wishes to visit is far greater than that of the ordinary motorist.

A discreet but easily recognisable car badge, issued, as Dr. Piper (July 2) suggests, by the Ministry of Pensions and National Insurance, would enable the police and the traffic wardens to identify the disabled motorist at a glance and assist him to find a suitable place to disembark.

Wilmslow, Cheshire. W. H. W. INMAN.

CORTICOSTEROIDS AND RAISED INTRACRANIAL PRESSURE

SIR,—In the matter of corticosteroids and raised intracranial pressure, it is surprising that so far only the negative aspects have been emphasised, and no attention has been paid to the much more interesting positive side. Thus, although it is undoubtedly true that prolonged steroid therapy,[5] or its sudden interruption,[6] may produce intracranial hypertension, the opposite is just as true and much more important—that is, intracranial hypertension, due to the usual causes (space-occupying lesions or inflammatory processes), is favourably influenced by corticosteroids.

In a series of tests in children (in whom hypertensive intracranial reactions are particularly severe and readily recognised) we found that 15–30 mg. of prednisone per day (1) noticeably reduced or completely abolished the outstanding symptoms (headache, vomiting and nausea, confusion, and clouding or impairment of consciousness) within three or four days; (2) reduced to a variable extent such symptoms as ataxia,

1. Silverman, M. *Brit. med. J.* 1959, i, 696.
2. Bethell, M. F. *ibid.* 1957, i, 30.
3. Seager, C. P., Foster, A. R. *ibid.* 1958, ii, 950.
4. Douthwaite, A. H. *ibid.* p. 1161.
5. Laurance, B. M., Matthews, W. B., Shephard, R. H. *Lancet*, 1960, i, 701.
6. Dees, S. C., McKay, H. W. *Pediatrics*, 1959, **23**, 1143.

papillœdema, and E.E.G. abnormalities, within ten to fifteen days; and (3) induced a strong feeling of wellbeing. The effects were at times so rapid and intense, especially in hypertension produced by tumours, that, both subjectively and objectively, the patient seemed to be almost completely cured. Naturally, in raised intracranial pressure produced by tumours, the improvement is only symptomatic and temporary: it has, however, the advantage of making pneumoencephalography, ventriculography, and operation safer and easier. In inflammatory hypertension corticosteroids not only give immediate relief of symptoms but also are useful therapeutically.

C. FAZIO
M. DE NEGRI
V. GRILLO
E. TARTARINI.

Clinica delle Malattie Nervose e Mentali e Instituto G. Gaslini, Genoa.

HEALING OF WOUNDS

SIR,—May I draw attention to the fact that thyroid medication in patients with breast cancer, after radical mastectomy, accelerates healing by producing more histamine in the skin?

These patients and patients with cancer of the female genitalia usually have a very low level of protein-bound histamine in the tissues.[1] If thyroid is given by mouth in increasing doses with histidine monohydrochloride, the histamine content of the tissues is increased. The skin of these patients was examined for histamine by Dr. W. S. Feldberg at the National Institute for Medical Research.[2] Wound healing in these patients proceeded quickly and satisfactorily and recurrences were prevented for many years.[3–5]

Thyroid emulsion and histidine injected together into and around the breast tumours led to their recession and sometimes even complete disappearance.

The histidine monohydrochloride was supplied by Roche of Basle. Further details will be published later.

These investigations took place in St. Bartholomew's Hospital, Rochester, and St. Mary's Hospital, London.

London, W.1. ALFRED A. LOESER.

ARTIFICIAL INSEMINATION

SIR,—My letter of Aug. 27 was a statement of fact: that A.I.D. was not adultery. Dr. Roberts' reply (Sept. 17) is an expression of opinion on the ethics of A.I.D.; an entirely different kettle of fish.

Crediton, Devon. L. N. JACKSON.

PRIMARY BILIARY CIRRHOSIS

SIR,—Dr. Mackay (Sept. 3) suggests that primary biliary cirrhosis is an autoimmune disease. He states: "Thus there is evidence that primary biliary cirrhosis should be classified within the group of tissue-destroying immunopathies".

The evidence that Dr. Mackay offers includes structural alterations in the liver, kidney, and stomach as noted in biopsies of these organs. These alterations consist of "lymphoid-cell" infiltrates and "destruction of tissue". The accompanying photographs of the stomach and kidney appear to us to be non-specific gastritis and a small focus of chronic pyelonephritis.

These non-specific alterations are frequently found in necrospy or biopsy material and, if one so desired, one could probably correlate them with virtually any unrelated disease process. In a review of our four necropsy cases of primary biliary cirrhosis, for the period 1945–55, we found no morphological alteration that allows the conclusion that there is a "multi-system disease" or an "immunopathy".

James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, Massachusetts. BENJAMIN CASTLEMAN
WALLACE A. JONES.

HÆMATEMESIS AND MELÆNA

SIR,—I am grateful to Dr. Chandler and his colleagues (Sept. 3) for their reference to my dissatisfaction over the radiological investigation of hæmatemesis, but I feel they do scant justice to the excellent work of Dr. Cantwell who devised the ward technique and already has published reports [1 2] on two series of patients. Dr. Cantwell in his last paper recorded 82% correct results in 200 patients, and this figure is being maintained in a further series which will be published when it is large enough.

Department of Diagnostic Radiology, The United Leeds Hospitals. A. S. JOHNSTONE.

TRIGEMINAL NEURALGIA

SIR,—The last three cases of true trigeminal neuralgia that have reached me have been associated with what I call the temporomandibular-joint syndrome, and each of the three cases has benefited from treatment of that condition.

It is easy to diagnose a temporomandibular-joint abnormality when there is audible clicking of the cartilage, or when the joint itself is tender to direct palpation, but it is not very generally appreciated that there is a syndrome which arises from relatively trivial damage to a temporomandibular joint which itself can remain painless.

My interest in the subject was first aroused by finding that almost always in cases of so-called atypical trigeminal neuralgia palpation of the deep aspect of the joint not only elicited the pain of which the patient complained but also resulted in his having an unusually uncomfortable day or two subsequently. It seemed to me that the pain I elicited arose from the anterior head of the lateral pterygoid muscle; and, after discussing the matter with my orthopædic colleague Mr. Denis Dunn, we began treating such cases first by injecting cortisone suspension into the muscle itself, and later (by analogy with the syndrome known as tennis-elbow) by injection into the temporomandibular-joint space. The results were rather mixed, but my present view is that the intra-articular injection is by no means easy and is not always successfully achieved, and my impression is that when the injection has proved easy and convincing the results have been equally satisfactory. Intra-articular injection of cortisone for the clear-cut temporomandibular-joint lesion is of course routine practice in many centres, but I have not discovered any reference to the syndrome associated with a joint which remains painless throughout. In some undiagnosed cases of facial neuralgia the site of the rather elusive pain may be found to be the lateral pterygoid muscle, which is almost inaccessible above and behind and lateral to the maxillary tuberosity.

In my experience these cases present with a history of pain which is localised most usually in the area superficial to the maxillary antrum but may sometimes be referred to the ear, the malar region, the angle of the mandible, or even the neck; but whatever the site complained of, the pain can be elicited by palpating the lateral pterygoid.

In the three cases of apparently true neuralgia referred to, the trigger zone was in the maxillary division of the fifth nerve, and palpation of the lateral pterygoid on the affected side merely produced pain but did not provoke a neuralgic paroxysm; the frequency and severity of the paroxysms decreased progressively when the joint-space was injected weekly.

I do not suggest that all cases of paroxysmal facial neuralgia are caused by the temporomandibular-joint

1. *Brit. med. J.* 1954, ii, 1380.
2. *J. Physiol.* 1954, **126**, 286.
3. *Brit. med. J.* 1955, ii, 143.
4. *Lancet*, 1955, i, 491.
5. *J. int. Coll. Surg.* 1958, **29**, 337.

1. Cantwell, D. F. *Brit. med. J.* 1957, ii, 941.
2. Cantwell, D. F. *Clin. Radiol.* 1960, **11**, 7.

syndrome, but I have the suspicion that at least some of my own patients who have in the past sustained alcohol injections had no more than a minor traumatic derangement of the mandibular joint.

I should like to acknowledge that in arriving at the conclusions which led to the treatment I am adopting at present I was helped and guided by my colleagues Dr. A. B. Pollard, Mr. J. B. M. Green, Mr. Denis Dunn, and in my own department by Mrs. E. B. Kendall.

Essex County Hospital,
Colchester. MICHAEL FROST.

OBSTETRIC FLYING-SQUADS

SIR,—Thank you for your comments on my letter of Sept. 3. While agreeing that early blood-transfusion may be advisable in some cases of hæmorrhage, I notice in the report on maternal deaths,[1] which you quote, that there is nothing to suggest that any of the mothers who died from hæmorrhage on the district were being given a plasma transfusion before the flying-squad arrived. Surely the decision to transfuse must be taken by the man on the spot, whereas the decision to change to whole blood may properly be made in consultation with the obstetrician in charge of the flying-squad. I imagine that similar procedures take place in hospital.

This same report, suggests that if the flying-squad had been called earlier to cases of obstructed labour or malpresentation, before the practitioner had made abortive attempts to deal with the abnormality, some mothers might not have died.

My object in writing to you, Sir, was to try and enlist your help in overcoming what can only be called lazy-mindedness in consultant obstetricians, who persist in the obviously false belief that there is some magical security in hospital buildings. Everyone knows that most maternity hospitals in this country are converted poor-law institutes and that the astonishing results produced in hospitals during the past thirty years in lowering maternal mortality are due to the men and women who work in them. Flying-squads provide a relatively cheap and easy method whereby these same men and women with their equipment can be transported to the mother's home.

In this way, as far as I can see, only in this way, the interest and the enthusiasm of the general-practitioner obstetrician will be provoked. He will learn to work as a member of a team and he will either subject himself to the disciplines of teamwork or will give up midwifery. I repeat: the only alternative is to deliver all women in hospital.

Cambridge. C. W. WALKER.

SIDE-EFFECTS OF LIBRIUM

SIR,—A new tranquillising drug, 7-chloro-2-methylamino-5-phenyl-3H-1, 4 benzodiazapine-4-oxide hydrochloride ('Librium'), is now available commercially. It has been widely advertised in terms of its taming effect on wild animals and claims have been made that it is of special value in controlling phobic and obsessional symptoms in psychoneurosis although the published evidence for this is slight.[2]

9 outpatients with phobic anxiety states and 6 with obsessional neuroses have been treated with this substance for three weeks. The dosage given was 10 mg. thrice daily for the first week and 25 mg. thrice daily thereafter. Only 3 of the 9 phobic patients and 1 of the 6 obsessional neurotics felt any subjective improvement.

Side-effects were seen in over half the patients. 2 felt drowsy on the smaller dose, 5 on the larger. 2 felt fatigued and apathetic, and dizziness and constipation were reported. 1 patient felt more energetic and 2 complained of severe irritability. After taking the drug for a week a schoolteacher struck his wife for the first time in the twenty years of their marriage. Of the 15 patients, 3 had to stop work because of the side-effects and 2 others refused to continue taking the drug after two weeks.

Although the number treated is small and the findings uncontrolled, the results are disappointing enough and the side-effects sufficiently troublesome to deserve attention. Other side-effects reported in trials in the United States have included dissociative reactions, hyperactivity, and ataxia.[3]

We feel justified in suggesting that the drug should be used with circumspection and scepticism until the results of controlled trials are available.

Southern General Hospital,
Glasgow. I. M. INGRAM
GERALD C. TIMBURY.

MORE CHROMOSOME ANOMALIES

SIR,—In a leading article [4] you discussed the relation between the so-called sex-chromatin or Barr bodies and X chromosomes. May I draw attention to some new facts and hypotheses that throw light on these problems?

Yerganian [5] recently found two types of X chromosomes in female Chinese hamsters (*Cricetulus griseus*), a predominant X_1 and a retarded X_2.[6] The predominant X_1 has a secondary constriction in a heterochromatic arm with a small pericentric euchromatic segment. The retarded X_2 has no secondary constriction and is strictly confined to the female. Ohno et al.'s [7] observation of different heteropyknosis in the X chromosomes of the female rat, only one of which forms the Barr body, seems to indicate that the X_1 chromosome of the Chinese hamster with its secondary constriction is the sex-chromatin-forming chromosome, but only so in the presence of an X_2 chromosome. This hypothesis implies a triheterosomic sex determination, normal females being X_1X_2 and normal males X_1Y.

Earlier observations already revealed more complicated heterosomes in some mammals,[8] but Yerganian et al.[6] now extend this hypothesis to most mammals and man. They discuss whether X_1 chromosomes can become differentiated to X_2 chromosomes so that an X_1X_1 combination results from fertilisation or alternatively X_2 differentiates to X_1 in X_1Y combinations. If Xs do not have the faculty to undergo this differentiation, what happens in the 50% of zygotes that are X_1X_1 or X_2Y? The authors are inclined to interpret X_1X_1 individuals as Turner's syndrome with 46 chromosomes and negative sex chromatin as observed by Ford et al.[9] Turner's with 45 chromosomes and absence of Barr bodies would be X_1O. The X_2Y combination would be a sex-chromatin-negative individual with the testicular feminisation syndrome. Chromatin positive (X_1X_2Y) and negative (X_1X_1Y) Klinefelter's syndrome are both understandable by this hypothesis.

In my opinion this hypothesis deserves further attention but fails to give a clear answer to the question of the often undesirable combinations as X_1X_1 and X_2Y in the event that X chromosomes do not have capacities for differentiation. Another hypothesis is based on the well-known fact that fertilisation in mammals and man takes place in the oocyte II stage of meiosis. The second polar body is expelled after sperm entrance.[10] I suppose that when the X_1 sperm enters the oocyte II the second meiotic spindle is oriented so that the X_1 half of the female nucleus is expelled and when the Y sperm enters the X_2-half is expelled. This implies that the oocyte II has a X_1X_2 constitution and undergoes postreduction so that in meiosis I one (or an uneven number of) chiasmas are formed between the centromeres and differential segments of the X chromosomal bivalent. The anomalies just mentioned, then, are caused by non-disjunctions and anomalous orientation of the second meiotic spindle. In my opinion this

1. Report on Confidential Inquiries into Maternal Deaths in England and Wales, 1955–57. H.M. Stationery Office, 1960.
2. Breitner, C. *Dis. Nerv. Syst.* 1960, **21** (suppl. 3), 31.
3. Tobin, J. M., Bird, I. F., Boyle, D. E. *ibid.* p. 11.
4. *Lancet*, July 23, 1960, p. 191.
5. Yerganian, G. *Cytologia*, 1960, **24**, 66.
6. Yerganian, G., et al. (in the press).
7. *Exp. cell Res.* 1959, **18**, 415.
8. Beatty, R. A. *in* Sex Differentiation and Development. London, 1960.
9. *Lancet*, 1959, i, 711.
10. Witchi, E. Development of Vertebrates; p. 43. Philadelphia, 1956.

hypothesis deserves no complicated sex-linkage mechanism as Yerganian et al. imply.

Further data are needed to elucidate the sex-determining mechanism in man. Yerganian's theory and my additional hypothesis may, I hope, stimulate further research.

Genetic Laboratory,
R.K. Universiteit,
Nijmegen, Netherlands. S. J. GEERTS.

PERPHENAZINE IN HUNTINGTON'S CHOREA

SIR,—Various attempts have been made during recent years to modify the uncontrolled movements of Huntington's chorea. The drugs used have been procaine amide,[1] reserpine,[2] and some of the phenothiazines (including chlorpromazine,[3] thiopropazate [' Dartalan '],[4] perphenazine [' Fentazin '],[5] and trifluoperazine [' Stelazine '] [6]). On the whole those drugs with the greatest tendency to produce parkinsonism are most effective for treating hyperkinetic symptoms. But one must remember that drugs such as perphenazine and trifluoperazine [7] are themselves liable to produce hyperkinesis.

I have used perphenazine in two cases because of its close chemical resemblance to thiopropazate, and because the first case I treated developed a rash with thiopropazate but not with perphenazine. Apart from this the results were equally good with either drug.

CASE 1.—A widow, aged 43, was admitted to hospital in April, 1955. There was no family history of nervous or mental disease. Movements typical of Huntington's chorea had begun 2 years previously and had become worse during the past 12 months. She could not manage to climb stairs, and she had often fallen off chairs, sustaining numerous injuries. She also had headaches, depression, and insomnia, and she had lost weight.

The following drugs were given with little or no effect: phenobarbitone gr. $^1/_2$ t.d.s., procaine amide tablets 0·5 g. t.i.d., reserpine 1 mg. t.d.s., benzhexol (' Artane ') up to 10 mg. t.d.s., and meprobamate 400 mg. t.d.s.

In October, 1958, she was given thiopropazate 10 mg. t.d.s., and the dose was gradually increased over 6 weeks to 30 mg. t.d.s. At this stage she was able to walk about without falling but some involuntary movements persisted when her attention was attracted. In February, 1959, a severe rash necessitated discontinuing this treatment, and she was given promethazine as tablets and ointment. The involuntary movements gradually returned, and the rash subsided.

Perphenazine was then given in doses of 8 mg. t.d.s. at first, and gradually worked up to 20 mg. t.d.s. She continued to take this dose until the end of October, and meanwhile the clinical improvement was the same as it had been with thiopropazate.

At about this time trifluoperazine became available, and it was thought that the same effect might be obtained with smaller doses than those needed with perphenazine. It was substituted without any intervening period, and the dose was raised gradually to 25 mg. b.d. by the end of the year. But both the staff and the relatives, who took her home on leave, agreed that she was not as well as she had been on either thiopropazate or perphenazine. She was accordingly given perphenazine again in January, 1960, and the dose was rapidly raised from 8 to 20 mg. t.d.s. She remained on this dose without ill effect until April, when she became unduly quiet and almost immobile. The perphenazine was therefore stopped until her " normal " choreiform movements returned. It was resumed 3 weeks later in a dose of 12 mg. t.d.s. and increased to 18 mg. t.d.s. in a week. She has taken this dose ever since and is leading a more active life than would otherwise have been possible. She has slight movements, but can get up and down two flights of stone steps to the occupational therapy department. Her speech is clear, but slow, and she takes an interest in her surroundings and relatives.

CASE 2.—A Ukrainian man, aged 42, who had been living in lodgings but could not be managed, was admitted to hospital in July, 1960. He could only walk with difficulty, and choreiform movements were very marked, especially when he was in bed and awake. His speech was indistinct.

Perphenazine was started in a dose of 8 mg. t.d.s., gradually increased to 20 mg. t.d.s. within 3 weeks, and later reduced to 18 mg. t.d.s. because of a fall in blood-pressure. The improvement in speech and gait, and diminution of movement, was similar to that noted in case 1. The patient became easily managed, and helped on the ward. He is at present working in the light industrial centre at the hospital.

A colleague who had charge of a chronic sick ward also gave perphenazine, in doses of 10–16 mg. t.d.s., to four very advanced bedridden cases with choreiform movements. One became worse, and the others did not improve.

The effects of perphenazine in the two cases of Huntington's chorea, however, seem to be sufficiently encouraging to warrant further study on a larger scale.

My thanks are due to Dr. Stanley Smith, medical superintendent, for permission to publish these cases, and for his coperation which enabled me to treat case 2; also to Dr. Douglas A. Kent for his helpful advice and by treating the advanced cases.

Lancaster Moor Hospital,
Lancaster. R. PAKENHAM-WALSH.

NEPHROTOXICITY OF ACETYLSALICYLIC ACID

SIR,—The belief that long-term abuse of analgesics may cause chronic interstitial nephritis with renal failure [1 2] has been widely accepted. Usually in such cases the patient has taken mixed analgesics containing phenacetin, acetylsalicyclic acid, acetanilide, or other drugs. Of these, phenacetin has been suggested as the nephrotoxic agent.

In short-term provocation experiments it was earlier shown that the urine-sediment count is increased during treatment with phenacetin, especially if phenacetin contaminated with acetic-4-chloranilide is used.[3] In order to elucidate whether the increase in the urine-sediment count is due to a specific nephrotoxic effect of phenacetin or is a non-specific feature, the provocation experiments have been extended to include provocation with acetylsalicylic acid, phenylbutazone, and acetanilide.

AVERAGE INCREASE IN ERYTHROCYTE AND LEUCOCYTE COUNT IN 12-HOUR URINE DURING TREATMENT WITH DIFFERENT ANALGESICS

Drug	Dose (g.) daily	No. of patients	Increase (%) in: Erythrocytes	Increase (%) in: Leucocytes
Pure phenacetin	3	11	16	38
Phenacetin contaminated with acetic-4-chloranilide ..	3	16	95	41
Acetylsalicylic acid	4	15	253	203
Phenylbutazone	0·8	10	39	36
Acetanilide	0·75	11	10	43

The daily intake was determined in accordance with the dosage clinically used. The sediment-count was determined for four days during which no drugs were given and for five days during treatment. For each patient the percentage change was calculated. The average rise for the patients in different groups is shown in the accompanying table, where our earlier results with pure phenacetin and phenacetin contaminated with acetic-4-chloranilide are included for comparison.

Much to our surprise acetylsalicylic acid and not phenacetin seems to cause the highest degree of kidney irritation. For a

1. Goldman, D. *Amer. J. ment. Sci.* 1952, **224**, 573.
2. Kempinsky, W. H., Boniface, W. R., Morgan, P. P., Busch, A. K. *Neurology*, 1960, **10**, 38.
3. Vaughan, G. F., Leiberman, D. M., Cook, L. C. *Lancet*, 1955, i, 1083.
4. Matthews, F. P. *Amer. J. Psychiat.* 1958, **114**, 1034.
5. Laricchia, R., Baseri, A. *Minerva Med.* 1958, **49**, suppl. 39, p. 1993.
6. Oliphant, J., Evans, J. I., Forrest, A. D. *J. ment. Sci.* 1960, **443**, 718.
7. Rees, L. *Brit. med. J.* Aug. 13, 1960, p. 522.

1. Spüler, O., Zollinger, H. U. *Helv. med. acta*. 1950, **17**, 564.
2. Spüler, O., Zollinger, H. U. *Z. klin. Med.* 1953, **151**, 1.
3. Harvald, B., Valdorf-Hansen, F., Nielsen, A. *Lancet*, 1960, i, 303.

definite evaluation of the relative toxicity of the drugs, comparative studies with all the drugs in the same person(s) are necessary. Such experiments are going on at present.

There is not necessarily any correlation between the increase in urine-sediment count during these short-term provocation experiments and the ability of the drugs to cause chronic interstitial nephritis after several years' administration. On the other hand these preliminary experiments call for caution in replacing phenacetin as an analgesic with acetylsalicylic acid, which has been the tendency in Scandinavia of late years.

Department of Medicine C,
Bispebjerg Hospital,
Copenhagen,
Denmark.

B. HARVALD
E. CLAUSEN.

SPIRITUAL HEALERS IN HOSPITALS

SIR,—*The Lancet* reaches me three months late but I hope that I can still join in the correspondence on this subject.

I feel that if we admit to the public for one moment that we do not know all the answers, that there are medical problems beyond our ken (whatever our private reservations may be), we shall be shaking the very foundations of our art. This is not to imply that spiritual healing, faith healing, psychotherapy (call it what you will) has no place in medicine. On the contrary. The point is that we ourselves, consciously or unconsciously, must rely to a tremendous extent on " spiritual healing ", and must jealously guard our own rights and duties in this respect. The good general practitioner (whether he realises it or not) is invested with the powers of a tribal medicine man, and therein lies much of his strength. The hospital, with its ritual and drama and hidden mysteries, undoubtedly also exerts a similar influence. As long as the patient has unbounded faith in the system, and as long as every person coming in contact with him, from the chemist-shop assistant to the ward charlady, overtly or tacitly strengthens his faith in the system, then he will derive as much benefit from our administrations as he can from any other source. Let us not deny the existence of this healing power—the charming away of warts is accepted fact, after all. Let us realise that we ourselves must rely for a large measure of our successes, however much it may go contrary to our " scientific " pride, on this same source of healing, whatever it may be. This is not simply a matter of assisting an " unqualified practitioner ", as though we were letting him prescribe, or give an anæsthetic. It is far more serious than that because to admit even the possibility that a spiritual healer can do something that we cannot do is to detract automatically, and in like measure, from our own effectiveness.

Noumea, New Caledonia. W. NORMAN-TAYLOR.

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P./1

SIR,—We appreciate the studies reported by Dr. Varadi and Mr. Elwis (Sept. 17) but wish to point out a serious misconception in their assessment of our recent investigation (Aug. 6). Our only object in this particular paper was to demonstrate that a reasonable hæmatological response could be obtained with very small doses of the B_{12}-peptide complex. We were not particularly concerned either with the optimum therapeutic dose or with the serum-vitamin-B_{12} levels.

As these two problems have been raised by Dr. Varadi and Mr. Elwis, however, it would assist us in understanding their work if they could tell us whether or not the patients they describe are the same ten to which Dr. Varadi refers in an earlier letter.[1] If they are the same patients, then might we ask whether all ten cases ultimately received 20 μg. a day of B_{12}-peptide as stated in the first communication, or did only one receive this amount, as stated in the second letter? Furthermore, the case which is reported to have relapsed on a dose of 100 μg. a day presumably did so before the earlier communication, since all ten cases had apparently been reduced to a daily dose of 20 μg. by that time. If this is true, was there any particular reason for failing to mention this relapse in the earlier letter, or was this relapse merely " a decline of the serum-B_{12} level " [1] and not a deterioration in the blood-picture?

Finally, as, apparently, the behaviour of the serum-B_{12} levels—and not the hæmatological responses—appears to be the main reason why they regard the B_{12}-peptide complex as unsafe, perhaps they would tell us what interpretation they put on their serum-B_{12} results, and what exactly is the scientific basis for such interpretation, when applied to this particular form of oral therapy.

St. Helens Hospital,
St. Helens.

F. S. MOONEY
J. G. HEATHCOTE.

ANÆSTHESIA FOR NEUROSURGERY

SIR,—As I have been almost exclusively concerned with neurosurgical anæsthesia for about twelve years, your editorial of Sept. 17 interested me considerably, particularly your references to the use of artificial respiration.

Since 1953 I have used controlled respiration in neurosurgery, employing a machine which produces a " positive-negative " pressure cycle. I have anæsthetised over 1000 cases in this way, the majority of them being major craniotomies, and over the past three years this has included posterior-fossa explorations.

There has arisen a disagreement between the senior neurosurgeons at Bristol and myself over the results achieved, which must of course be taken into account when considering the pros and cons of the technique. However, personal observation, and reassessment of my results, has convinced me of the considerable benefits achievable by proper use of controlled respiration, and I believe that Dr. Galloon will endorse this from his own experience.

I have only some small comments about your editorial.

During operations conducted under mechanical controlled respiration, I have often observed rhythmic cyclical changes in the physical state of the exposed brain, occurring at the same rate as the rate of artificial ventilation.

At a point corresponding with the subatmospheric phase of the respirator, at which the recorded intratracheal pressure was reduced to about 4 cm. of water below the barometric pressure, cortical veins were seen to collapse, and to refill with blood as the pressure rose. There is of course a time lag, or phase shift, produced by the resistance and reactance of the venous system extending between thorax and peripheral cortical veins. Moreover, the brain itself may be seen to pulsate at the respiratory rate, and quite independently of the pulsations due to the cardiac cycle. This cyclical fall in venous pressure, if not watched and moderated, can result in the drawing of air into vessels.

I have the greatest respect for Dr. Hunter, but your editorial suggests that he denies that a change in intracranial pressure can accompany and be produced by artificial respiration. In my experience, and the experience of my surgical colleagues, considerable changes can be produced in this way.

Dr. Hunter would not disagree that inadequate ventilation, and/or a raised mean respiratory pressure, can produce very quickly a considerable increase in cerebral congestion, as he must have had occasion to observe this.

Additional observations of the pressure changes accompanying mechanical respiration were made in my cases, by observing the rise and fall of cerebrospinal fluid level in both lumbar and intraventricular drainage systems; the fluctuations in pressure with each cycle seldom exceed a few millimetres of water, but are readily visible.

1. Varadi, S. *Brit. med. J.* 1959, ii, 756.

The longer-term changes in C.S.F. tension which accompanied changes in the mean respiratory pressure were also observed, and these could amount to several centimetres of water.

In an individual case, whether the brain movements accompanying respiration, or the C.S.F. pressure changes, are the most striking, depends on the degree of overriding congestion, or decompression, already present. If the dura is widely opened, and the brain is relaxed, it can move freely, and will be seen to do so with respiration, whether artificial or natural. If it is engorged, but the drained ventricle is not collapsed, or the dura is closed, or only slightly open (as round the margin of a small parietal meningioma, for example), the brain movements are restricted, but fluctuations in blood content in the venous tree are transferred to the C.S.F., and the fluctuations will be very clear.

The displacement of C.S.F. occurs presumably in the same way as the displacement during a Queckenstedt test.

The phenomena are not always observable, and they are masked effectively if congestion and tension are already high. In my experience they may be seen in at least three-quarters of all "cold" frontal and parietal craniotomies anæsthetised in this way. When present they are quite evident, and do not require the eye of faith!

Dr. Galloon has, I believe, confirmed to his own satisfaction that intracranial tension can be controlled by the correct use of controlled respiration, though I have not heard from him personally. A recent paper from Oxford would suggest that Mr. Pennybacker is inclined to agree.

It is of course true that the introduction, from the United States, of the use of intravenous urea has proved of very great value in the control and treatment of cerebral swelling due to trauma, whether surgical or otherwise. There do seem to be two possible disadvantages to be considered when deciding treatment with urea solutions.

One is its effect on the peripheral venous system: one case of extensive necrosis has arisen in my experience, though not fortunately in one of my patients, and there have been several cases of thrombophlebitis. The other is the possibility of reactionary œdema at a later stage.

Controlled respiration is not capable of reducing disastrous congestion, as is urea, once it has occurred, but it does seem to control its development during surgery; and in cases which are not seriously compressed preoperatively, and in which induction has not produced congestion, it maintains a relaxed brain, with freedom from venous congestion and oozing, without apparently any risk of subsequent reactionary œdema. The most effective control of cerebral œdema seems to be anticipatory. It is far more effective to act early, and hence to avoid being faced with an emergency, and the use of controlled respiration seems to give this early action in many cases; though it has been my practice to give hypertonic sucrose at induction to all cases where the intracranial tension is known to be raised, or there is papillœdema of a high order.

Cases of frontal craniotomy for chiasmal and pituitary exploration do not show the orbital œdema in the postoperative period which was previously believed to be inseparable from frontal craniotomy.

The major source of doubt as to the effectiveness of the method probably lies with the surgeon, not the anæsthetist. Such has certainly been my experience.

Whether or not traumatic œdema develops either operatively or postoperatively depends to a large extent upon the detailed surgical technique, as well as upon the pathological changes. In neurosurgery, no two cases are truly alike, and it seems that no two neurosurgeons wish to follow the same detailed technique. Meticulous gentleness is a variable quality in the best of us, and yet in removing a tumour, the superfluous destruction of a draining vein may change the whole picture, and the whole prognosis. A relaxed brain, with a relatively bloodless field, changes quite quickly to a state of severe congestion ("acute cerebral œdema") without any assistance from the anæsthetist, who may now find his careful attempts to provide safe and easy operating conditions nullified!

The state of the brain is so dependent upon the factors of surgery, anæsthetics, and pathology that objective assessment of the value of any method can be difficult, without prolonged experience and the ability to learn from it.

The observations outlined here were reported by me to the Society of British Neurological Surgeons in November, 1956. The technique of anæsthesia was described then, and also in a letter to the *British Journal of Anæsthesia* in November, 1957.

Bristol. PETER L. F. MORTIMER.

THE FEMALE PROSTATE

SIR,—Mr. Thomas Moore [1] has excellently discussed the problem of lower urinary obstruction in the female. I think he is also to be congratulated for his initiative and courage in stating: "It is unfortunately still traditional for urinary symptoms in the female to lead to a gynæcological consultation . . ." In Israel, too, dysuric females are often treated by gynæcologists and other doctors not specially trained in urology.

Antibiotics may temporarily ameliorate certain symptoms, but may also mask certain lesions and lead to irreversible renal damage.

Admittedly transurethral resection of the bladder neck in properly selected cases will give excellent results in both men and women with lower urinary obstruction. But the resectionists' main concern is to avoid injury to the external sphincter. In the male this sphincter is protected by the verumontanum, which serves as a landmark. In the female the external sphincter is an ill-defined structure and there are no such landmarks. Transurethral resection in the female is a rather delicate procedure in which an extra bite too far distally may transform obstruction into incontinence.

It seems to me that conservative treatment including persistent urethral dilatations should perhaps be tried first, reserving transurethral or open bladder-neck resection for cases in which it fails. In 26 female patients who have come under my care operation (transurethral resection) has been needed in only 3.

I agree entirely with Mr. Moore that bladder-neck obstruction in women is not as uncommon as it is believed to be. I feel that its frequency depends on the care with which it is sought. A thorough urological examination, including voiding cystography, may reveal not only unsuspected obstruction of the bladder outlet but also its disabling sequelæ.

Tel Aviv. HERZL KOOK.

ENDEMIC CRETINISM AND DEAF-MUTISM

SIR,—I have been waiting for an opening such as that provided by your leader of July 23, and I thank you for having provided it. Among other questions raised by your thoughts is the question of the genesis of endemic cretinism and deaf-mutism. Although I have nowhere come across a plausible explanation of the widely disparate frequencies with which deaf-mutism accompanies endemic goitre in different regions, there seems to be an explanation of these divagations in certain data collected by D. Danielopolu and his collaborators in Rumania.

I have them in book form (*Les Thyroidies Endémiques et Sporadiques* published in Paris undated by Masson) but the book refers to previous publication in numbers 1 and 3 of the *Bulletin de l'Académie de Médecine de Roumanie* for 1937. On

1. *Lancet*, 1960, i, 1305.

p. 18 of Danielopolu's book, he defines what he means by *sourds muets* in the book by classifying their condition as *Surdi-mutité thyroidienne* under *Affections paragoitreuses* which is the fourth listing under *Thyroidies*. The data which I should like to present are scattered from pages 50 to 63, and are those relating deaf mutism as just defined to economic status (see accompanying table). By economic status, I mean what

GOITRE AND DEAF-MUTISM IN RUMANIA

Area	Approximate total population	No. of subjects examined	No. of goitres found	No. of deaf mutes with an economic status of		
				Good	Average	Poor
Moldavitza valley	2000	1621	924	0 (208)*	0 (220)	9 (491)
Vatra-Moldavitza commune ..	1400	1381	523	0 (78)	0 (116)	2 (374)
Frumosuol commune.. ..	1500	1238	603	0 (39)	0 (63)	7 (454)
Vama commune	3000	2331	1087	1 (116)	0 (146)	16 (797)

* Figure in parentheses is number of uncomplicated goitres (*goitres normothyroidiens*) found in each group.

Danielopolu calls *l'état matériel et l'alimentation quantitative:* this is obviously closely connected with nutritional status.

These data suggest strongly that deaf-mutism accompanies endemic goitre when the goitre is associated with poor nutritional status. This suggestion is given further weight by Greenwald's observation [1] that endemic goitre seems to be accompanied by a high incidence of deaf-mutism in certain parts of South America and Europe, but not in the United States of America or Canada.

Whippany, New Jersey. MARSHALL E. DEUTSCH.

1. *A.M.A. Arch. Otolaryngol.* 1959, **70**, 541.

Obituary

FRED THOMPSON BOWERBANK

K.B.E., M.D. Edin., F.R.C.P.E., F.R.A.C.P.

Major-General Sir Fred Bowerbank, consulting cardiologist to Wellington Hospital and director-general of the New Zealand Army and Air medical services during the late war, died on Aug. 25.

He was born in 1880 at Penrith in Cumberland and educated at Edinburgh University, graduating M.B. in 1904. Soon afterwards he settled in New Zealand and, after a period in general practice, specialised in cardiology. In the 1914–18 war he served with distinction with the New Zealand Expeditionary Force in Europe. He remained in the Territorial Force and became D.M.S. (Army and Air) for New Zealand. On the outbreak of the war in 1939 he was made D.G.M.S. and remained head of the medical services until he retired in 1947. He was a fellow of the Edinburgh and Australasian Colleges of Physicians. He was appointed O.B.E. in 1917 and promoted K.B.E. in 1946. He was also a grand officer of the Order of Orange-Nassau.

A colleague writes:

"Bowerbank was a man of wide interests and, outside his professional life, was a leader in such societies as Toc H, Crippled Children, and the Red Cross. He had a distinguished personal appearance and was a man of great charm and had a host of friends. He was one of the best known and most influential medical men in New Zealand over the past forty years."

Sir Fred Bowerbank married in 1907 Miss Muriel Pick, who survives him.

HERBERT LEVY

M.D. Berne, M.R.C.P.

Dr. Herbert Levy, senior hospital medical officer at Bethnal Green Hospital, died at his home in London on Sept. 6, at the age of 56.

He studied medicine in Berlin and Berne and graduated M.D. at the University of Berne in 1934. After holding hospital appointments in Germany, including a clinical assistantship with Prof. P. R. Richter at the Hospital in Friedrichshain, Berlin, Dr. Levy came to Britain as a refugee. He took the Scottish triple qualification in 1935, and for a time he practised in Streatham. At the beginning of the war he joined the London County Council hospital service and became assistant medical officer at Lambeth Hospital. Later he joined the staff of the Bethnal Green Hospital. He took the M.R.C.P. in 1945.

A colleague writes:

"Dr. Levy was a true physician with a wide knowledge of Anglo-American and European writings on clinical medicine. A fine diagnostician, with a rare discerning mind, he rose to the challenge of a difficult and unusual case, but his first consideration was always the patient and not the case. He had many friends, not only among his colleagues and patients, but also in the worlds of art and literature. He especially loved France and her art and literature. Though he was aware of the seriousness of his condition for many years, he never let this interfere with his work, his devotion to his friends and their problems, and his zest for life."

Dr. Levy leaves a wife and a young son.

MELANIE KLEIN

Mrs. Melanie Klein, who died in London on Sept. 22 at the age of 78, was an original and creative psychoanalyst, who developed a technique of play-analysis for the treatment and study of small children.

She was born in 1882 in Vienna, of Jewish parents. Her youthful ambition was to be a doctor but an early marriage and family duties intervened. Later her interest in the workings of the mind, particularly in children, drew her to the then new study of psychoanalysis, and she trained as an analyst under Ferenczi and Abraham. She acknowledged the contribution each made to her development, but it was from Abraham that she received most insight and stimulus toward her original work.

Child analysis was in its early stages in Berlin in 1921 when she began to develop her technique for the psychoanalysis of young children. She came to England in 1926 to continue her work here at Ernest Jones' invitation. Her published work included *The Psycho-Analysis of Children* (1932), *Envy and Gratitude* (1957), and *The Narrative of a Child Analysis* (in the press).

S. I. writes:

"Melanie Klein saw that the play of even very small children reveals the content of their unconscious minds in essentially the same way that Freud had seen that verbal 'free association' revealed the hidden processes of the adult mind. She also found it possible to relieve anxiety, even in children of only 2–3 years old, by putting into words for them what she saw of their unconscious fantasy life; showing that Freud's discovery of the therapeutic effect of interpretation can be directly applied to children. Her technique of play-analysis has proved invaluable as a method of therapy and research. Serious psychological disturbances, including psychotic illness, in children became accessible to treatment.

"She worked out the details of early infantile methods of dealing with anxiety caused by powerful and conflicting impulses of love and hatred and saw that they were an extension of Freud's dynamic concept of the unconscious into the earliest stages of human life. She studied the ways in which the loving and creative aspects of human personality can be overwhelmed, inhibited, or distorted by aggressive impulses, in children and adults. Her recognition that very early infantile

stages of emotional development can continue to exist within the adult made possible greater understanding of the origin of psychotic illnesses and their relationship to more normal states of mind. With this knowledge came improved skill in the psychoanalytic treatment of serious personality disorders and psychoses in adults. In addition the influence of her work has been felt in the handling of mentally ill patients, the care of babies and young children, and in the management of schoolchildren as in the less obviously related fields of human creative thought and expression. Her great intellectual vigour, clarity, and coverage persisted throughout her life, and she was able to see patients and write until a few weeks before her death.

"Many people reacted to her work with fear, disgust, and hostile criticism. They were provoked particularly by the details of aggressive fantasies in very young children and by the idea of their persistence in adults. It was one of the tragedies in the fruitful life of this indomitable Freudian that the opposition was so bitter at times. But her work had a profound influence on the British Psycho-Analytic Society and on an increasing number of psychoanalytic groups. She was also able to establish a small but vigorous and original group of colleagues. She may have sometimes been irked or wearied by opposition but was never surprised by it, for she shared with Freud a deep understanding of the fear of the unknown and in particular a respect for the human being's fear of the unconscious forces within his mind. She combined in her small frame feminine charm and interests with unusual intellectual gifts which she had the strength of purpose to use. The importance of her scientific discoveries may be partly beyond general comprehension at the moment. But history places people in their right perspective; and though Melanie Klein was accorded relatively little credit in her life time, the importance of her work will be appreciated realistically in the future.

"What can be the effect of one woman courageous enough to look into the human mind in its developmental stages and see its struggles with aggression? There is the encouragement we gain from the example of someone engaged throughout a long life in the unremitting search for scientific truth, however frightening or unpalatable. Also there is the hope that increased understanding of their unconscious impulses will eventually enable human beings to preserve from their own destructiveness all that they value most."

Sir HAROLD GILLIES

R. E. R. writes:

"In the last five years of his life, Sir Harold Gillies visited India a number of times and helped to establish plastic surgery units as well as visiting centres of medical teaching and research. Though he could not give much time he had done a great deal of operating and teaching in the units and regarded them as his own creations and their staff as his pupils."

A memorial service to Sir Ernest Rock Carling will be held at St. Margaret's, Westminster, at NOON on Monday, Oct. 3.

Appointments

Birmingham School Health Service:

TODMAN, R. C. F., M.B. Edin.: school M.O.
TYLER, JANET B., M.B. Lond.: school M.O.
WILLIAMS, DAVID, M.B. N.U.I., D.A.: school M.O.

Colonial Appointments:

BOWMAN, R. K., M.R.C.S., D.P.H.: chief M.O., Gilbert and Ellice Islands.
CHUI WAN CHEONG, J. P. A. F., M.B., D.OBST.: M.O., Mauritius.
CLYDE, D. F., L.M.S. Nova Scotia: specialist malariologist, Tanganyika.
FOWLER, A. F., M.R.C.S., D.T.M. & H., D.P.H.: principal M.O., Uganda.
HEARD, R. G. P., M.B. Dubl., D.T.M. & H.: senior M.O. (clinical), Tanganyika.
HOPWOOD, B. E. C., M.R.C.S., D.P.H., D.I.H.: deputy chief M.O., Uganda.
OAKEY, J. S., M.B. Sydney, D.T.M. & H., D.P.H.: senior M.O., Tanganyika.
RUNCIMAN, CHARLES, M.B. W'srand, D.P.H., D.T.M. & H., D.I.H.: senior M.O. (administrative), Tanganyika.
SWEENEY, T. K., M.B. N.U.I., D.T.M. & H., T.D.D.: senior M.O., Tanganyika.
WONG, HOK NIN, M.B. Hong Kong: principal medical and health officer, Hong Kong.

Notes and News

RHODESIA AND NYASALAND TEACHING HOSPITAL AND MEDICAL SCHOOL

REAFFIRMING in Salisbury on Sept. 23 his Government's decision to establish a multiracial teaching hospital and medical school attached to the University College of Rhodesia and Nyasaland,[1] the Federal Prime Minister, Sir Roy Welensky, said:

"Doctors are in short supply throughout the world and in addition existing medical schools are becoming overcrowded with fewer and fewer places available to students from abroad. In clear terms, the position today is that we can no longer continue to expect other countries to train our medical students nor expect other countries to supply the bulk of our demand for medical, nursing, and allied, professional people. The time has come to provide for our own needs.

"After most careful consideration, the Rhodesia Medical School Planning Committee have concluded that the advantages of having a medical faculty and teaching hospital in close proximity are so great that despite some increased capital cost for a hospital of this nature the building of a teaching hospital is justified. Therefore I am able to announce tonight that the Federal Government have accepted the obligation to build, equip, and staff a teaching hospital of some 350 beds on a twenty-five acre site adjacent to the University College at Salisbury.

"It is estimated that buildings will cost about £1·4 million and that the annual operating cost including capital redemption will be in the nature of £0·5 million. My Government accepts this considerable responsibility in order to hasten and assure the progress of medical and health services of the Federation. . . . The establishment of a medical school—a million pound project with an annual recurring charge of some £235,000 only slightly offset by revenue from fee-paying students—may seem a formidable task and indeed it is, but I am happy to be able to acknowledge considerable support already promised to the University Medical School, particularly from the Nuffield Foundation itself which has made an offer of no less than a quarter of a million pounds.

"At the same time, the University of Birmingham has offered to sponsor medical degrees and I believe I speak for the whole Federation when I say how deeply appreciative we are of this action, which will enable our young medical students to receive degrees which will rank among the best, and to be taught by men and women of the highest quality and qualifications."

OUTBREAK OF TUBERCULOSIS IN AN IMMUNISED COMMUNITY

IN one of the northernmost counties of Sweden, Warfvinge [2] says, at least 90% of the children born since 1940 have had B.C.G. vaccination and about 10% of them have been revaccinated at school age, because the tuberculin reaction had faded out. In these circumstances the population, numbering about 5000, might well expect not to be troubled by tuberculosis. Indeed in 1955–56 a survey by mass radiography was fully reassuring. But in the spring and early autumn of 1958 a crop of pleurisies in 9 youngsters started a hunt for suspects. This extended gradually from members of the patients' family to fellow workers, shops, dairies, and other sources of food; yet the culprit could not be found. As the number of new cases rose, mass radiography was again undertaken, being applied wholesale in November, 1958. Even so the mystery might have remained unsolved had not a youth of 19, who had eluded radiography, volunteered for clinical examination because of an obstinate cough. His sputum teemed with tubercle bacilli, and both lungs were the seat of cavernous tuberculosis. A devotee of dancing, he had also engaged in kindred activities calculated to promote a liberal exchange of germs. By last April the number of people he had infected was 27—of whom 20 had pleurisy and all but 2 were between sixteen and twenty-three years of age. All 27 have fared well, and it is perhaps significant that miliary and meningeal tuberculosis have been conspicuous by their absence. 17 of the 20 patients with pleurisy had been vaccinated with B.C.G. once or oftener.

1. See *Lancet*, July 16, 1960, p. 139.
2. Warfvinge, L. *Kvartals Skrift Svenska Nationalföreningen Mot Hjärt-Och Lungsjukdomar*. 1960, **55**, no. 2.

University of London

The following degrees have been awarded:

M.D.—J. A. M. Ager, George Belyavin, David Burman.
M.S.—I. F. K. Muir.

Royal College of Surgeons of England

On Thursday, Oct. 20, Prof. J. F. Nuboer will give a Moynihan lecture. He will speak on recurrent peptic ulcer after gastrectomy. On Thursday, Oct. 27, Dr. Cuthbert Dukes will give a Thomas Vicary lecture. His subject will be genetics in relation to surgery. Both lectures will be given at 5 P.M. at the college, Lincoln's Inn Fields, London, W.C.2.

Royal College of Surgeons of Edinburgh

On Wednesday, Oct. 19, at 3.30 P.M., at the college, Mr. Eric Samuel will give a lecture on mechanical syndromes following partial gastrectomy.

Royal College of Obstetricians and Gynæcologists

At a meeting of council on Sept. 24, with Sir Andrew Claye, the president, in the chair, the following were admitted to the membership:

Augustus Amartei Armar, Christian Bam, Dhirendra Nath Banerjee, Sreemanta Kumar Banerjee, N. M. D. Blyth, Pauline M. Bousquet, A. H. Bradfield, G. F. Bradfield, I. T. Brake, Tancred Busuttil, I. E. Cary, K. L. Collins, Joan M. Curtis, L. S. Deane, Marie T. D'Netto, R. F. Heys, Ma Hla-Kyi, Florence P. Isaiah, W. I. H. Johnston, J. B. Jones, Karapati Kanakadurgamba, William Kelso, J. F. Kemp, J. F. Leeton, J. L. Marcus, J. M. Mistry, W. M. Moore, E. D. Morris, Barun Kumar Mukherji, Olusola Adewole Ojo, P. R. B. Pedlow, W. S. E. Perera, Walter Pollard, Doreen Rothman, Anjul Kumar Sinha, Sarel Johannes Smal, A. M. Smith, H. J. Solomon, Bruce Sutherland, T. E. Torbet, A. R. Trist, W. L. Whitehouse.

St. Mary's Hospital, London

Dr. G. B. Mitchell-Heggs has been appointed dean of the Medical School in succession to Mr. A. G. Cross.

College of General Practitioners

On Sunday, Nov. 20, at 10 A.M., at the Wellcome Building, Euston Road, London, N.W.1, the college will hold a symposium on mental health and the family doctor. In the morning there will be a discussion on emotional disorders in general practice (Dr. E. C. Hamlyn, Dr. Michael Balint, and Dr. David Stafford-Clark), and in the afternoon on the psychoses in general practice (Dr. J. R. Rees, Dr. John Horder, and Dr. Russell Barton). Further particulars may be had from the secretary of the college, 41, Cadogan Gardens, Sloane Square, London, S.W.3.

Ophthalmological Society of the United Kingdom

The annual congress of this society will be held from April 13 to 15 at 1, Wimpole Street, London, W.1, when Mr. F. W. Law will give his presidential address. Miss Ida Mann has chosen for the subject of her Bowman lecture Climates, Cultures, and Eye Diseases. The programme will also include a discussion on neovascularisation in ocular disease (Prof. Norman Ashton and Mr. Redmond Smith) and a symposium on the late complications of aphakia (Mr. A. J. B. Goldsmith and Mr. J. R. Hudson). Further particulars may be had from the society, 47, Lincoln's Inn Fields, W.C.2.

Sir Andrew Claye is visiting Nigeria at the invitation of the Federal Government in connection with the independence celebrations.

On Friday, Oct. 14, at 3 P.M., at the University of Leeds, Sir Robert Aitken will give the inaugural lecture to the faculty of medicine. His subject will be Medicine Today and Tomorrow.

Dr. G. M. Carstairs is to give a lecture at the Marlborough Day Hospital, 38, Marlborough Place, St. John's Wood, London, N.W.8, on Monday, Oct. 3, at 8.15 P.M. He is to speak on recent trends in American Psychiatry.

At a meeting of the Cambridge Medical Society on Wednesday, Oct. 19, at 8.30 P.M., at Owen Webb House, 1, Gresham Road, Cambridge, Dr. L. S. Penrose will speak on mongolism.

The second edition of the *International Catalogue of Mental Health Films* has been published by the World Federation for Mental Health. The editor is Dr. T. L. Pilkington and copies (21*s.* each) may be obtained from the Federation, 19, Manchester Street, London, W.1.

At a meeting of the Medical Electronics Discussion Group on Friday, Oct. 7, at 6 P.M., at the Institution of Electrical Engineers, Savoy Place, London, W.C.2, the subject for discussion will be nerve-endings. The opening speakers will be Dr. O. C. J. Lippold and Dr. D. R. Wilkie.

The autumn dinner of the Wessex Rahere Club will take place at the Grand Spa Hotel, Bristol, on Saturday, Oct. 29, under the chairmanship of Dr. Russell Grant. Membership of the club is open to all Barts men practising in the West Country. The hon. secretary is Mr. A. Daunt Bateman, 11, The Circus, Bath.

The Medical Research Council have reprinted from their annual report for 1958–59 reviews of research on selected medical and biological subjects which they think will interest scientific and lay as well as medical readers. Copies of *Current Medical Research* (3*s.* 6*d.*) may be had from H.M. Stationery Office.

The National Committee on Maternal Health, Inc. (2, East 103rd Street, New York 29, N.Y.), have published a *Selected Bibliography of Contraception: 1940–1960*. The editor is Dr. Christopher Tietze. Free copies will be supplied to schools, libraries, and governmental and non-profit organisations.

Semipermanent exhibitions will be held during the autumn at the Institute of Dermatology, Lisle Street, London, W.C.2. The first, from Oct. 3 to 7, will be by Dr. Henry Haber on normal skin.

The Hospitals Symphony Orchestra, which meets on Mondays at 7.30 P.M. in St. Thomas House, Lambeth Palace Road, London, S.E.1, has vacancies in all string sections and in some of the wind and brass sections. Further particulars may be had from Miss M. A. Whipp, South Western Hospital, Landor Road, S.W.9.

Births, Marriages, Deaths

DEATH

MACINTYRE —On Sept. 23, Eneas John MacIntyre, M.D. Glasg., formerly M.O.H. for Sutton and Cheam and Banstead, at the age of 62 years.

Diary of the Week

OCT. 2 TO 8

Monday, 3rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *United Services.* Air Commodore G. H. Morley: Role of Plastic Surgery in the Royal Air Force.

Tuesday, 4th

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. Wilson, F.INST.P.: Nuclear Physics.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. Ian McCaul: Involuntary Movement.

Wednesday, 5th

ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine.* Prof. K. J. Franklin: Charles I and Harvey.
8 P.M. *Surgery.* Prof. C. Lambert Rogers: Surgical Problems of the Cervical Spine.
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
2 P.M. Prof. G. M. Bull: Place of Chemical Pathology in Medicine.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Histology of Normal Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton Hospital, S.W.3
5 P.M. Dr. J. R. Bignall: Problems of Lung Cancer.
UNIVERSITY OF LEEDS
5 P.M. (General Infirmary at Leeds) Miss U. M. Lister: Endometriosis.
6 P.M. Sir Andrew Claye: Dyspareunia.

Thursday, 6th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Dr. W. H. McMenemey: Immunity Mechanisms in Neurological Disease. (Presidential address.)
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P.M. (Rembrandt Hotel, Thurloe Place, S.W.7). Mr. Harvey Jackson: Pathways to the Brain. (Presidential address.)

Friday, 7th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. Dr. R. S. Allison, Dr. J. H. D. Millar, Dr. Henry Miller, Prof. C. E. Lumsden, Dr. E. J. Field, Dr. J. B. Finean, Prof. G. Payling Wright, Prof. R. H. S. Thompson, Prof. S. Refsum (Oslo), Prof. G. I. Scott, Dr. Rowland Farrell: Disseminated Sclerosis and Allied Conditions. (All-day symposium.)
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Prof. L. N. Pyrah: Aspects of Renal Calculi.
4 P.M. Prof. G. M. Bull: Regulation of Water and Salt Excretion.

Saturday, 8th

BRITISH ASSOCIATION OF PHYSICAL MEDICINE
10.15 A.M. (Royal Sussex County Hospital, Brighton). Provincial autumn meeting.

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